Pharmacovigilance Guideline

for

Marketing Authorisation Holders

in Armenia

Revision 1.0

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Table of Contents

Chapter I: Introduction

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem."

Republic of Armenia legislation requires marketing authorization holders (MAHs) and the National Regulatory Agency (NRA; the Scientific Centre of Drug and Medical Technology Expertise after Academic E. Gabrielyan) to follow a number of pharmacovigilance processes after medicines and vaccines have been authorized to monitor the safety of these products, and if necessary take action to protect public health.

Order of the Ministry of Health of the Republic of Armenia N23-N of May 17 2017 places statutory obligations on all Marketing Authorization Holder (MAH) whose products are authorised and marketed in Armenia to have in place a system for documenting and conducting the following:

- ✓ Have a system in place for conducting pharmacovigilance activities in Armenia and have systems in place to ensure the quality of the pharmacovigilance system
- ✓ To hold and submit a Pharmacovigilance System Master File (PSMF) to document the pharmacovigilance system and its quality system appoint a QPPV/LPPV
- ✓ Risk management systems
- ✓ Management and reporting adverse reactions of medicines
- ✓ Products Periodic safety update reports (PSURs)
- ✓ Post authorization safety studies
- ✓ Signal management
- ✓ Safety communication
- ✓ Risk minimization measures

Detailed guidance on the regulatory requirements for Pharmacovigilance system and their Quality system as well as guidance on the purpose, structure and content of the pharmacovigilance activities within the Pharmacovigilance system is provided in the Eurasian Economic Commission (EEC) Good Pharmacovigilance Practice guidelines [insert reference] and applicants and MAHs should continue to ensure that they are fully compliant with the EEC GVP Modules.

This guideline has been prepared by the National Pharmacovigilance Centre (the PV department of the NRA) to supplement the EEC GVP Modules with information about additional local requirements for MAHs in Armenia as well as practical information to support regulatory submission of the required Pharmacovigilance documents to the NRA in Armenia.

Chapter II: Pharmacovigilance Systems and their quality systems, including the Pharmacovigilance System Master File (PSMF)

A pharmacovigilance system is defined as a system used by an organization to fulfill its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance. A pharmacovigilance system, like any system, is characterized by its structures, processes and outcomes. Each specific pharmacovigilance process, including its necessary structures is described in Eurasian Economic Community (EEC) Good Pharmacovigilance Practice (GVP) Modules.

The Pharmacovigilance System Master File (PSMF) is a detailed description of the Pharmacovigilance System for one or more medicinal products of the MAH. The PSMF should document compliance of the MAH's pharmacovigilance system with the requirements laid out in EEC GVP and may be requested and assessed by the NRA during marketing authorization application(s) or post-authorization.

Through development and maintenance of the PSMF, the MAH should be able to

- ☐ Gain assurance that a pharmacovigilance system has been implemented in accordance with the requirements
- ☐ Confirm compliance in relation to the system
- ☐ Obtain information about deficiencies in the system, or non-compliance with the requirements
- ☐ Obtain information about risks or actual failure in the conduct of specific aspects of pharmacovigilance.

The information gathered through maintenance of the PSMF will contribute to the appropriate management of and improvement(s) to the pharmacovigilance system.

The MAH should ensure that it has an appropriate Pharmacovigilance System in place in order to assume responsibility and liability for its products on the market and to ensure that appropriate action is taken when necessary.

Applicants and MAHs in Armenia should ensure that a quality assured Pharmacovigilance System is established and maintained in accordance with the guidance provided in EEC GVP, "Requirements for a quality system".

The Armenian NRA requires all applicants and MAHs to maintain and make available upon request a PSMF. EEC GVP Module II provides detailed guidance on the requirements for a PSMF, including its maintenance and content.

In general, the content of the PSMF should reflect global availability of safety information for medicinal products authorized in Armenia, presenting information on the pharmacovigilance system applied at global, regional and local levels.

For Armenia, the PSMF should provide a clear illustration of the key elements of both global pharmacovigilance system and national pharmacovigilance sub-system, highlighting the role of QPPV/LPPV, which pharmacovigilance activities are carried out in Armenia, which are carried out in the headquarters/globally and how they integrate

together. EEC PSMF can be used if MAH acts in other EEC Countries.

In accordance with EEC GVP, the PSMF must contain the following:

- ☐ QPPV details
- ☐ Organizational structure of the applicant/MAH
- ☐ Sources of safety data
- ☐ Computerized systems and databases relevant for PV
- ☐ PV Processes
- ☐ PV system performance
- ☐ Quality System
- ☐ Annexes (lists of products)

The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements.

The PSMF shall be continuously accessible to the QPPV and to the NRA on request. The PSMF shall be located (physically) either at the site where the main Pharmacovigilance activities of the marketing authorization holder are performed or at the site where the QPPV operates.

Practical guidance: submission and update of the PSMF

The PSMF must be submitted with all marketing authorization applications to the NRA. A summary of the MAH pharmacovigilance system (Name of the QPPV, QPPV contact details and location of the PSMF, letter of appointment from the company, CV, list of products covered by the company, tasks and responsibilities) can be included instead of the PSMF on condition that the PMSF will be provided at the request of the NRA.

- ☐ When the PSMF is requested by the NRA the document should be submitted within 7 calendar days. However, MAHs should be aware that immediate access to the PSMF by the NRA may also be required.
- ☐ The PSMF should be submitted to the NRA electronically to admin@pharm.am in searchable PDF format in Armenian, Russian or English.
- ☐ In case of significant updates or changes to any section of PMSF, a notification letter and details of the updates should be submitted.
- ☐ When the QPPV and related contact details change or when the location of the pharmacovigilance system master file changes, the marketing authorisation holder is required to submit the appropriate variation application(s) to the national competent authorities

Chapter III: Qualified person responsible for Pharmacovigilance (QPPV)

Statutory requirements

There are currently no statutory requirements for an applicant/MAH to have at its disposal a Local person for Pharmacovigilance (LPPV) in Armenia.

Non-statutory requirements in Armenia

The Armenia NRA requires that as part of its pharmacovigilance system the local MAH should have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance resident in Armenia (QPPV). For multinational MAHs a EEC QPPV should be appointed according to EEC GVP. If EEC QPPV is not located in Armenia, LPPV should be appointed in addition to perform activities on a local level. LPPV responsibilities should be described in PSMF, and/or MAH Quality System Documents if MAH has representative office in Armenia, or in PV Agreement if LPPV activities are outsourced.

When submitting an application for new Pharmaceutical Product authorization the Applicant, should submit a PSMF and submit proof that the services of a Qualified Person Responsible for Pharmacovigilance (QPPV) in Armenia are in place. In case QPPV is not located in Armenia, LPPV(s) contact details should be also provided to NRA.

The name and 24 hours contact details of the nominated QPPV and his\her alternate during absence should be submitted.

The MAH shall ensure that the QPPV/LPPV has acquired adequate theoretical and practical knowledge for the performance of PV activities. The QPPVs should have a minimum of bachelor degree in pharmacy, medicine or related area.

The QPPV shall be responsible for the establishment and maintenance of the marketing authorization holders' Pharmacovigilance System and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements.

Practical guidance on submission PMSF

The applicant/MAH should provide the following in order to inform Armenian NRA on QPPV appointment:

1. QPPV Letter of appointment from the company
2. QPPV CV
3. QPPV contact details
4. List of products covered by the company in Armenia
5. Tasks and responsibilities
6. LPPV contact details (if applicable)

The information must be submitted during the authorization with the dossier and post-authorization phase if anything is changed.

Document must be submitted electronically searchable in Armenian, English or

Russian to admin@pharm.am.

Chapter IV: Risk Management Systems

A Risk Management System (RMS) is 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 activities and interventions.

A Risk Management Plan (RMP) is a detailed description of the risk management system and contains:

1. A safety specification which provides information about the known safety profile of the medicinal product, with emphasis on important identified and important potential risks and any important missing information about the products safety profile; and which of these safety concerns/areas of missing information need to be managed proactively or further studied;
2. A pharmacovigilance plan which provides details of any pharmacovigilance activities to characterise and quantify clinically relevant risks, and to identify new adverse reaction;

3. A risk minimisation plan which provides details of what risk minimisation measures are necessary and how these will be implemented, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

As knowledge regarding a medicinal product's safety profile increases over time, so will the Risk Management Plan change.

A RMP / or updated RMP must be submitted:

- ☐ for new molecules should be submitted with the registration application
- ☐ for new combination of known molecules with the registration application
- ☐ for new innovator, biological, and biosimilar should be submitted with

the registration application

- ☐ for registration (re-registration), if there is an existing RMP for a medicinal product
- ☐ upon NRA request

Applicants/MAHs should ensure that RMPs submitted to the NRA in Armenia are drafted in accordance with the detailed guidance provided in EEC GVP on Risk Management Systems. International applicants/MAHs may provide RMP written in accordance with applicable EU GVP guidelines.

In the case of initial submission for registration of generic products for which RMP has been introduced for the original product, modules CII – CV of the safety specifications for RMP may be omitted.

If the RMP was previously submitted by the MAH during the registration procedure for the active substance, any subsequent RMP submissions should be submitted as an update after registration of the product.

If no changes have been made to the RMP since the last submission, the MAH may submit a letter explaining the absence of changes.

Practical guidance on submission and update of RMPs

- ☐ RMP should be submitted in searchable PDF format in Armenian, Russian or English.
- ☐ Electronically on email address: admin@pharm.am

Chapter V: Collection, management and submission of reports of suspected adverse reactions to medicinal products

This section refers to measures to collect, collate and submit reports of suspected adverse reactions to the NRA as the national competent authority.

Applicants should refer to the detailed guidance on work with the information on suspected adverse reactions to medicinal products in EEC GVP. The Following individual case safety reports should be submitted to NRA:

- ☐ Local reports on serious and non-serious adverse reactions;

Foreign reports on serious unexpected adverse reactions.

- ☐ Expedited reporting of local serious adverse reactions and foreign serious unexpected adverse reactions is required as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the MAH. Local reports of non-serious adverse reactions should be reported in 90 calendar days, whether expected or not. Non-serious ADRs cases from other countries related to products registered in Armenia should be included in the periodic safety update report.

The regulatory reporting time clock is considered to start on the date when any personnel of the MAH first receive a case report that fulfills minimum criteria as well as the criteria for expedited reporting. In general, this date should be considered day 0.

When additional medically relevant information is received for a previously reported case, the reporting time clock is considered to begin again for submission of the follow- up report.

SUSARs from clinical trials should be reported

- ☐ up to 7 calendar days from the date of receipt of information, in case of fatal or life-threatening SUSARs
- ☐ up to 15 calendar days from the date of receipt of information in case of other SUSARs

It is recommended that the Medical Dictionary for Regulatory Activities (MedDRA) be used for coding medical information.

Practical guidance on submission of reports

Reports should be sent electronically in Armenian, Russian or English.

Local reports should be in ICH E2B (R3) form, CIOMS, in regulatory reporting form or company form which contains all necessary information. International cases should be submitted in CIOMS forms. All reports should be sent to vigilance@pharm.am. For local cases the subject of an email should indicate local cases.

Chapter VI: Signal Detection & Management

Signal detection refers to the process of looking for and/or identifying signals using data from any source. The signal management process refers to a set of activities performed to determine whether based on examination of data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed. It also includes related recommendations, decisions, communications and tracking.

The signal detection and management process is described in the EEC Good Pharmacovigilance Practice, module IX.

MAHs shall:

- ☐ controls all available data and information on signals;
- ☐ monitors all data appearing in its database, voluntarily monitors NCA and other available databases and perform international signal detection. All signals should undergo a validation process taking into account the components of the information provided, indicated in subsection 9.1.3.3 of EEC GVP Rules;
- ☐ validate all detected signals and report them to the competent authorities in PSUR on an ongoing basis
- ☐ notified the competent authorities in the event that an emergency safety problem is identified as a result of signal detection activities;

- ☐ cooperates with the competent authority in the implementation of procedures for the evaluation of signals by providing additional information upon request;
- ☐

Chapter VII: Periodic Safety Update Reports (PSURs)

- ☐ Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorization holders at defined time points during the post-authorization phase.
- ☐ The required format and content of PSURs are based on those for PSUR described in the EEC Good Pharmacovigilance Practice as well as for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH -E2C (R2) guideline.

Timelines for PSUR submission:

PSUR submission is mandatory for the registration and reregistration for medicinal product in Armenia.

For the medicinal products not included in the aforementioned list, the periodicity for submission of PSURs is as following: new molecules registered in Armenia PSUR should be submitted as follows:

- ☐ every 6 months from the international registration date for the first 2 years;
- ☐ annually over the next 2 years;
- ☐ further - every 3 years;
- ☐ On request of national Regulatory authority

The deadline for submission of PSUR is not more than 90 calendar days from the date of the end of data collection.

PSUR should be submitted in PDF searchable format in Armenian, Russian or English an Armenian regional appendix should be submitted with the PSUR (if applicabe).

The appendix contains following information:

- ☐ Proposals for product information amendments
- ☐ Supportive documentation for amendments to product information
- ☐ Descriptions of ongoing variations

Practical guidance for submission of PSUR

PSURs and all supporting documents should be submitted electronically as searchable document by mail to admin@pharm.am

Chapter XIII: Safety communication

Safety communication module provides guidance to MAH, national medicines authorities on how to communicate and coordinate safety information. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the safe and effective use of medicines, preventing harm from adverse reactions and contributing to the protection of patients' and public health. Safety communication is a broad term covering different types of information on medicines, including statutory information as contained in the product information (i.e. the Summary of Product Characteristics (SmPC), Package Leaflet (PL) and the labelling of the packaging).

The primary target audiences for safety communication should be patients and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products

As primary target audiences, healthcare professionals play an essential role. Effective safety communication enables them to give clear and useful information to their patients, thereby promoting patient safety and confidence in the regulatory system.

Patient, consumer and healthcare professional organizations can play a role as multipliers as they can disseminate important safety information to target audiences. The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for

amplifying new and important information on medicines. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from the national medicines authorities in addition to the information they receive from other sources, such as from the MAHs.

More detailed described in EEC GVP module11

Content of safety communication:

- ☐ any emerging important information which affects the benefit-risk ratio under any conditions of use of an authorized medicinal product;
- ☐ the reasons for initiating the safety communication in a form that is understandable to the target audience;
- ☐ the necessary recommendations for health care providers and patients related to the safety issue that is being communicated;
- ☐ information of the agreement between the MAH and Regulatory authority on the provision of safety information (if necessary);
- ☐ information on all proposed changes in the information on the medicinal product (for example, in SPC or PIL);
- ☐ a bibliography or references to sources where more detailed information can be found on the specific safety aspect indicated in the safety communication;
- ☐ a reminder of the need to report suspected adverse reactions to the Regulatory authority through the national system of spontaneous reporting.

Safety communication should not be misleading and should be presented objectively. Safety communication should not contain any materials and messages that may be advertising or other information aimed at promote the medicine.

Means of Safety Communication are:

- ☐ Direct healthcare professional communication (DHPC)
- ☐ Communication for non-professionals
- ☐ Press communication
- ☐ Website
- ☐ Other web based communications
- ☐ Bulletins and newsletter
- ☐ Inter authority communication
- ☐ Responding to enquiries from the public

Practical guidance on submission of safety communication

All safety information prior to be communicated by MAH should be submitted to NRA for approval. As the official language in RA is Armenian all the safety communication must be submitted in Armenian together with original (English or Russian) version. After the approval communication the Armenian version must be disseminated by MAH though the appropriate health facilities Russian and English versions might be communicated together with Armenian version.

DHPC should be provided according to EU DHPC format.

While submitting a DHPC to the NRA, a plan for distribution of the DHPC have to be submitted as well.

MAH is responsible for dissemination of the safety communication.

All approved safety communications will also be posted on Regulatory authority web site.

Regulatory authority can in its turn decide the mean of safety communication for MAH depended of safety concern and target audience.

MAHs are responsible for the evaluation of the effectiveness of safety communication.

Chapter XIII: Risk minimization measures

Planning and implementing risk minimization measures and assessing their

effectiveness are key elements of risk management. Risk minimization measures may consist of routine risk minimization or additional risk minimization measures. Routine risk minimization is applicable to all medicinal products, and involves the use of the followingtools.

- the Summary of Product Characteristics (SmPC);
- the Package Leaflet (PL);
- the labelling;
- The legal (prescription) status of the product.

Risk minimization measures aim to optimize the safe and effective use of a medicinal product throughout its life cycle. The risk-benefit balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimizing benefit, through targeted patient selection and/or exclusion and through treatment management (e.g. specific dosing regimen, relevant testing, patient follow-up). Risk minimization measures should therefore guide optimal use of a medicinal product in medical practice with the goal of supporting the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring. Additional risk minimization activities should only be introduced when they are deemed to be essential for the safe and effective use of the medicinal product and should be developed and provided by suitably qualified people.

Educational programs

Educational programs are based on targeted communication with the aim to supplement the information in the summary product characteristics (SmPC) and package leaflet. Any educational material should focus on actionable goals and should provide clear and concise messages describing actions to be taken in order to prevent and minimize selected safety concerns.

The aim of an educational program

The aim of an educational program is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimizing risk. Educational materials should therefore be built on the premise that there is an actionable recommendation for targeted education and that applying this measure is considered essential for minimizing an important risk and/or for optimization of the risk-benefit balance. Ideally, educational materials should be available in a range of formats so as to ensure that access is not limited by disability or access to the internet. When feasible the appropriateness of the tool and media for the target audience (e.g. suitable language, pictures, diagrams, or other graphical support) should be user tested in advance, in order to optimize the success of the implementation phase.

The content of any educational material

Should be fully aligned with the currently approved product information for a medicinal product, such as the SmPC and package leaflet, and should add rather than duplicate SmPC and package leaflet information. Promotional elements, either direct or veiled (e.g. logos, product brand colors, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimization.

Educational tools

Should focus on clearly defined actions related to specific safety concerns described in the RMP and should not be unnecessarily diluted by including information that is not immediately relevant to the safety concern and that is adequately presented in the SmPC or package leaflet. Educational tools should refer the reader to the SmPC and the package leaflet. In addition to an introductory statement that the educational material is essential to ensure the safe and effective use and appropriately manage important selected risks, elements for inclusion in an

educational tool could provide:

- guidance on prescribing, including patient selection, testing and monitoring;
- guidance on the management of such risks (to healthcare professionals and patients or carers);
- guidance on how and where to report adverse reaction of special interest.

Educational tools targeting healthcare professionals:

The aim of any educational tool targeting a healthcare professional should be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (how to manage adverse reactions) associated with the medicine and the specific important risks needing additional risk minimization measures, including:

- selection of patients;
- treatment management such as dosage, testing and monitoring;
- special administration procedures, or the dispensing of a medicinal product;
- Details of information which needs to be given to patients.

The format of a particular tool will depend upon the message to be delivered. For example, where a number of actions are needed before writing a prescription for an individual patient, a checklist may be the most suitable format. A brochure may be more appropriate to enhance awareness of specific important risks with a focus on the early recognition and management of adverse reactions, while posters for display in certain clinical environments can include helpful treatment or dosage reference guides. Other formats may be preferable, depending on the scope of the tool.

Educational tools targeting patients and/or carers:

The aim of tools targeting patients should be to enhance the awareness of patients or their carers on the early signs and symptoms of specific adverse reactions causing the

need for additional risk minimization measures and on the best course of action to be taken should any of those symptoms occur. If appropriate, a patient's educational tool could be used to provide information on the correct administration of the product and to remind the patient about an important activity, for example a diary for posology or diagnostic procedures that need to be carried out and recorded by the patient and eventually discussed with healthcare professionals, to ensure that any steps required for the effective use of the product are adhered to.

Patient alert card

The aim of this tool should be to ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate. The information should be kept to the minimum necessary to convey the key minimization message(s) and the required mitigating action, in any circumstances, including emergency. Ability to carry with ease (e.g. can be fitted in a wallet) should be a key feature of this tool.

Practical guidance on submission of risk minimization measures

All educational materials prior to be disseminated should be approved by Regulatory authority. As the official language in RA is Armenian all the educational materials must be in Armenian, however Russian and English versions might be communicated together with Armenian version.

MAH is responsible for dissemination of the educational materials. All approved educational materials if needed will also be posted on Regulatory authority web site.

References

1. Law on medicines of RA
2. Good pharmacovigilance practice EEC
3. Order of Minister
4. ICH guidelines
5. EMA