

**BOARD OF THE MINISTRY OF HEALTH OF THE REPUBLIC OF  
AZERBAIJAN**

**RESOLUTION**

**№ 39**

*Baku city*

*August 25, 2020*

**on approval of the “Guidelines for Good Pharmacovigilance Practice”**

Approved by the Decree of the President of the Republic of Azerbaijan dated May 25, 2006 No. 413 in order to implement item 2.1.23 of the “Rules of pharmacovigilance of medicines” approved by the Resolution of the Cabinet of Ministers of the Republic of Azerbaijan No. 503 dated December 25, 2019 Guided by item 14.5 and part 19 of the “Regulations on the Ministry of Health of the Republic of Azerbaijan” Board of the Ministry of Health of the Republic of Azerbaijan

**Resolved:**

1. To approve "Instructions on Good Pharmacovigilance Practices" (is applied).
2. To instruct the Department of Internal Control (S.Safarov) to submit this resolution to the Ministry of Justice of the Republic of Azerbaijan for inclusion in the State Register of Legal Acts of the Republic of Azerbaijan within 3 days.
3. Control over the implementation of the decision to assign to the deputy ministers.

Chairman of the Board,  
Minister

Ogtay Shiraliyev

Board of the Ministry of Health  
of the Republic of Azerbaijan,  
approved by Resolution No. 39,  
dated August 25, 2020

## **Regulation on Good Pharmacovigilance Practice (GPP)**

### **1. General provisions**

1.1. Instruction on Good Pharmacovigilance Practice (hereinafter - the Instruction) No. 503 of the Cabinet of Ministers of the Republic of Azerbaijan dated December 25, 2019 Prepared and implemented in accordance with the “Rules of Pharmacovigilance of Medicines” (hereinafter the Rules) approved by the decision and in order to control the safety of medicines, timely identification of all changes in the benefit-risk ratio of medicines, determines the rules of conduct.

1.2. The Law of the Republic of Azerbaijan “On Medicinal Products”, other laws of the Republic of Azerbaijan, decrees of the President of the Republic of Azerbaijan, decisions of the Cabinet of Ministers of the Republic of Azerbaijan, this Instruction and other normative legal acts of the Republic of Azerbaijan are followed in determining requirements for pharmacovigilance documents.

### **2. Basic concepts**

2.1. The basic concepts used in this Instruction have the following meanings:

2.1.1. **Date of registration of medicines in the European Union (EU) (EU reference date; Union reference date)** - the date of the first registration in the EU of a medicinal product containing the same active ingredient or combination of the same active ingredient or the same active ingredient; or, if it is not possible to determine this date, the date of the first known registration of a medicinal product in question or a combination of the active substance in question;

2.1.2. **Adverse event (AE)** - an undesirable medical condition that occurs in a patient who is prescribed a medicine, the medicine under study, or in a volunteer involved in a clinical trial, and there is no absolute cause-and-effect relationship with the treatment applied; (All undesirable and undesirable changes (eg, abnormal laboratory results), symptoms, or illnesses that occur during the use of a medication, whether or not are associated with the medication, may be considered an undesirable event.)

2.1.3. **Adverse reaction** - an unexpected adverse reaction of the human body when using a medicine in the dose specified in the instructions for use in accordance with Article 1.0.17 of the Law of the Republic of Azerbaijan "On Medicinal Products". An adverse reaction is an unwanted and unexpected reaction of the human body caused by the use of a medicine. The term "response" here means that

there is at least an acceptable probability of a cause-and-effect relationship between the medicine and the adverse event.

Undesirable reactions that occur when a person is exposed to an over-the-counter or over-the-counter medication, or when a person is exposed to an occupational medicine. Over-the-counter use of a medicine means overdose, misuse, abuse and medical misconduct;

2.1.4. **minimum criteria for reporting** - important information that must be reported in connection with an event when reporting additional impact. This information includes information about the person sending the notice (name, surname, position, address), information about the patient, at least one identified side effect and at least one medication;

2.1.5. **serious adverse reaction** - according to sub-clause 2.1.3 of the Regulation, which causes death during the use of the medicine, endangers human life, placement in a treatment-and-prophylaxis facility or prolongation of stay in a treatment-and-prophylaxis facility, temporary disability any adverse reaction that results in loss or disability (disability) or congenital anomaly or developmental defect;

To determine the severity of an event, the characteristics or consequences of the side effect must be considered. Medical and scientific judgment should be sought when deciding whether a side effect is a serious side effect. Some medical conditions may put the patient in a dangerous situation or may require intervention to prevent one of the above consequences. Such important medical conditions should be considered a "serious side effect." Examples include emergency and urgent medical care for allergic bronchospasm, or the appointment of intensive care at home, convulsions that do not lead to hospitalization, or medicine dependence or medicine abuse. When a contagious disease is suspected to be transmitted through medication, this should also be considered a serious side effect.

2.1.6. **ongoing alarm** - signals that are still being evaluated in the period of information lock in periodically updated security reports;

2.1.7. **overdose** - a dose taken as a result of the use of the medicine or its accumulation in the body, in excess of the maximum single or daily dose recommended in the instructions for use of the medicine approved by the Agency; A clinical evaluation should be performed to determine whether the dose is exceeded.

2.1.8. **missing information** - lack of safety information on the characteristics of the use of the medicine in clinically significant or certain patient groups;

2.1.9. **quality of a pharmacovigilance system** - all elements of the pharmacovigilance system used to achieve results in accordance with the objectives of pharmacovigilance within the projected capabilities;

2.1.10. **quality system of a pharmacovigilance system** - a part of the pharmacovigilance system that expresses the organizational structure,

responsibilities, operations, processes, resources, management of resources and documents and compliance with regulatory norms;

2.1.11. **Company core safety information (CCSI)** - in the main information document on the safety of the licensee and on the licensee's medicines, prepared by the licensee and submitted to the competent authorities of the countries where the medicine is sold at his request all available information (except for information changed at the request of the competent authorities);

VET is information that identifies the status of listed and unlisted side effects for the purpose of compiling a periodically updated safety report of the medicinal product, but does not contain expected and unexpected side effects that are not required to be reported immediately.

2.1.12. **Company core data sheet (CCDS)** - a document developed by the license holder, which, along with safety information, contains instructions for use of medicines, dosage, pharmacological properties and other information related to the medicine;

2.1.13. **safety concern** - important identified risk, significant potential risk, or missing information;

2.1.14. **target population (treatment target population)** - patients to whom the medicine is prescribed taking into account the indications and contraindications for use of the medicine in the approved instructions for use;

2.1.15. **misuse of a medicinal product** - intentional and inappropriate use of a medicinal product outside the instructions;

2.1.16. **Risks related to the use of a medicinal product** - any risks arising in connection with the quality, safety and effectiveness of a medicinal product in the health of patients and the population and risks that may cause adverse effects on the environment;

2.1.17. **abuse of a medicinal product** - permanent or one-time excessive use of a medicinal product accompanied by undesirable physiological or psychological effects;

2.1.18. **closed signal (closed signal)** - a signal that the evaluation of the periodically updated security report has been completed during the reporting period;

2.1.19. **occupational exposure to a medicinal product** - exposure of a person to a medicinal product during professional or other activities;

2.1.20. **identified risk** - an undesirable outcome of pharmacotherapy in which sufficient evidence has been obtained that a medicine may be associated with a suspected medicine;

2.1.21. **potential risk** - an undesirable outcome of pharmacotherapy in which there are doubts as to whether it is related to the medicine and this connection has not yet been confirmed;

2.1.22. **significant identified risk and significant potential risk** - identified or potential risks that may affect the benefit-risk ratio of the medicine or have significant consequences for the health of the population;

2.1.23. **reference safety information of a medicinal product** - information entered into the CCSI by the holder of a medicinal product safety certificate;

2.1.24. **risk minimization measures (risk minimization measures; risk minimization activity)** - complex measures aimed at preventing or reducing the likelihood of side effects associated with exposure to the medicine, reducing the severity of side effects;

2.1.25. **healthcare professional** - a doctor, pharmacist, dentist, paramedic, nurse and midwife involved in the reporting of suspected side effects;

2.1.26. **direct healthcare professional communication (DHCP)** - a warning letter sent directly to the medical staff by the license holder or the Institution to take certain preventive measures related to the medicine and to adapt their daily activities to the new situation; (This letter is not identical to the letter answered in response to inquiries from medical staff)

2.1.27. **signal validation** - the process of evaluating the signal support information found in order to confirm that the existing documents contain sufficient evidence of a new potential cause-and-effect relationship or an existing cause-and-effect relationship and thus justify further investigation of the signal;

This assessment should take into account the validity of the evidence, its clinical relevance, and the known cause-and-effect relationship.

2.1.28. **signal management process** - to determine whether there are new risks associated with an active substance or medicine or whether there is a change in known risks based on ICSRs, active control systems or data collected from research, literature and other data sources process;

Alarm identification, signal analysis, signal evaluation, signal validation, priority setting, and activity planning are components of this activity.

2.1.29. **completed clinical trial** - a clinical trial or trial in which the final report is ready;

2.1.30. **international birth date (IBD)** - the date of issuance of the first registration card for the sale of a medicine in any country;

2.1.31. **development international birth date (DIBD)** - the date of the first approval (or permit) for interventional clinical research / testing of a medicine in any country;

2.1.32. **validated signal** - signals that contain sufficient evidence that the information supporting the signal identified during the validation process of the signal, the possible cause-and-effect relationship of the signal or a certain relationship has acquired a new dimension and therefore provides a basis for further investigation of the signal;

2.1.33. **data lock point** - the date of completion of data collection in the PSUR;

2.1.34. **inspection** - an official inspection by the Authority of documents, records, employees, systems, locations and facilities of the licensee or the organization authorized by him to perform pharmacovigilance obligations on the pharmacovigilance system;

2.1.35. **audit (audit)** - a systematic, systematic, independent and documented process initiated by the licensee to obtain and objectively evaluate audit information characterizing the pharmacovigilance system;

2.1.36. **solicited sources of individual case safety reports** - containing clinical trials / studies, registers, post-registration programs for individualized use of the medicine, patient support and other disease monitoring programs, data collection systems organized at the request of patients or treating physicians, or data collection on the effectiveness of treatment and patients' dependence on treatment.

2.1.37. **quality control and assurance of the pharmacovigilance system** - monitoring, evaluation, ensuring the effectiveness and compliance with the established requirements of the structural elements and processes of the pharmacovigilance system.

2.1.38. **Medication error** - any intentional mistake of a medical worker, patient or consumer in prescribing, releasing, dosing or injecting / taking a medicine.

2.1.39. **Development safety update report (DSUR)** - a format and content of a periodically updated safety report of a developed medicine.

2.1.40. **off-label use** - the use of a medicine for medical purposes, intentionally, not in accordance with the instructions for use of the medicine.

2.1.41. **ongoing clinical trial**

2.1.42. **non-interventional study (non-interventional study)** - research / testing that meets the following requirements:

a) the medicine is prescribed in accordance with the instructions for use;

b) the decision to prescribe a particular treatment to a patient is not made in advance according to the study protocol, but is in accordance with accepted practice and the appointment of a medicine is clearly separated from the decision to include the patient in the study;

c) no additional diagnostic or screening procedures are applied to patients, and epidemiological methods are used to analyze the data obtained.

### **Notes**

1. Non-interference research / experiments are determined by the methodological approach used, not by scientific purposes.

2. Non-interventional studies / trials include a review of medical records or a database survey that already describes all the events reviewed (for example, case-control studies, cross-sectional and cohort studies). Non-interventional studies also include studies that involve the collection of initial data provided that the above conditions are met (for example, registers where records of routine treatment are recorded and prospective non-interventional studies).

3. In this context, blood samples may be taken, interviews and surveys may be conducted as part of regular clinical practice.

2.2. The terms used in this Instruction may have different meanings in other legal acts.

### **3. Quality system requirements**

#### **3.1. Quality system**

3.1.1. The quality system is an integral part of the pharmacovigilance system. The quality system should cover the organizational structure, scope, procedures, processes and resources of the pharmacovigilance system. The quality system should include Good management of resources, verification of compliance with the requirements of the legislation and management of documentation.

3.1.2. The quality system provides the following:

- building the structure of the system and planning integrated and coordinated processes (quality planning);
- fulfillment of tasks and obligations on the quality system (quality control);
- checking and evaluating the effectiveness of the structure and processes of the quality system (quality assurance);
- regulation and improvement of the structure and processes of the quality system (quality improvement).

3.1.3. The general objectives of the quality system in the pharmacovigilance system are as follows:

- fulfillment of pharmacovigilance obligations and requirements of the legislation;
- elimination of undesirable consequences related to the use of registered medicines;
- ensuring the use of medicines when the benefits outweigh the risks;
- support for the protection of the patient's health and public health.

#### **3.2. Principles of Good Pharmacovigilance Practice**

3.2.1. The following principles shall be observed in the development of systems and processes for the implementation of the general quality objectives set forth in paragraph 3.1.3, as well as in the performance of all tasks and obligations:

- Ensuring full compliance with the requirements of patients, medical staff and society related to the safety of medicines;
- providing effective management for the application of the quality system and staff motivation;
- Involvement of all employees of the organization (enterprise) in the process of supporting the pharmacovigilance system within the obligations;
- Involvement of all employees of the organization in the process of continuous improvement of the quality of the pharmacovigilance system;

- organization of tasks set before the database and pharmacovigilance system in the form of structures and processes in such a way as to ensure active, risk-based and uninterrupted work on pharmacovigilance;
- registration and evaluation of all available evidence on the benefit-risk ratio, as well as all information that may affect the use of medicines for this ratio and subsequent decisions;
- support the development of effective cooperation between producers, licensees, authorities, medical institutions, patients, medical staff, scientific organizations and other stakeholders in accordance with the requirements of applicable law.

### **3.3. Persons responsible for the quality system**

3.3.1. Ensuring the operation of the pharmacovigilance system in accordance with the requirements of the quality system is the responsibility of all specialists involved in the organization of the quality system. It is necessary to ensure a systematic approach to the proper application and support of the quality system. The enterprise must be provided with an experienced and trained specialist with a sufficient number of relevant qualifications to carry out the required amount of work on pharmacovigilance at the required level.

3.3.2. Systematic approach to quality assurance should be provided by business leaders. Within the framework of the functions of ensuring a systematic approach, the heads of enterprises are responsible for:

- ensuring that the quality system is documented in accordance with existing requirements;
- ensuring Good control and documentation of all changes in the pharmacovigilance system and the quality system of pharmacovigilance;
- ensuring the possibility of training;
- provision of required resources (including necessary rooms, equipment, etc.);
- Carrying out regular assessments of the operation of the pharmacovigilance system, including the integrated quality system, with the confirmation of its effectiveness. If necessary, the required corrective and preventive measures should be taken;
- Ensuring the existence of an effective mechanism for the implementation of appropriate measures in case of detection of changes in the safety profile of medicines being prepared / released;
- ensuring timely detection of non-compliance with the quality requirements of the pharmacovigilance system and, if necessary, corrective and preventive measures;
- Ensuring regular audits of the system.

### **3.4. Staff training**

3.4.1. The ability to implement pharmacovigilance processes and ensure the required quality of the results obtained is directly related to the availability of a sufficient number of knowledgeable, qualified and trained personnel.

3.4.2. A training plan for pharmacovigilance specialists should be developed and implemented at the enterprise. The training should include general introductory training and follow-up training throughout the work cycle, in accordance with the functions performed and the tasks assigned. The training should be aimed at improving relevant professional skills, applying scientific achievements to practice and procedures, ensuring that all specialists meet the requirements for qualification, professional skills, knowledge of pharmacovigilance and understanding of the procedures performed. All specialists must be trained to perform the procedures prescribed when detecting changes in the safety profiles of medicines.

3.4.3. The training process should include elements of verifying the learning outcomes in order to perform pharmacovigilance functions and achieve the required level of understanding.

3.4.4. Specialists of other departments are required to be trained in certain aspects of pharmacovigilance, whose activities in the enterprise may affect the performance of the pharmacovigilance system and the performance of pharmacovigilance functions. These activities include, but are not limited to: clinical research / testing, grievance redressal, medical information preparation, sales and marketing, registration documentation, legal issues and auditing.

### **3.5. Means and equipment for pharmacovigilance**

3.5.1. It is related to the implementation of pharmacovigilance processes and the achievement of the required level of quality of the results obtained, as well as the provision of the system with the necessary tools and equipment used in these processes.

3.5.2. Means and equipment must be located, installed, adapted and ready for operation in accordance with the objectives of the quality system of the pharmacovigilance system. Means, equipment and their functional functions, which are important for the implementation of pharmacovigilance, must be properly inspected, qualified and / or validated to confirm their suitability for the intended purpose. A documented risk assessment should be used to determine the extent of the inspection, qualification or validation. This method of risk management should be applied throughout the life of the tools and equipment, taking into account factors such as the impact on patient safety and data quality, as well as the complexity of the relevant tools and equipment.

### **3.6. Ensuring compliance with the requirements of the legislation by cardholders**

3.6.1. In order to ensure compliance with the requirements of the legislation, licensees must carry out the following special processes on the quality system:

- Regular monitoring of pharmacovigilance data, development and application of risk minimization measures if necessary, Good assessment of safety information

regardless of the source of entry (by patients, health workers and pharmacists, published in the medical literature, identified in post-registration studies) ;

- scientific evaluation of all information on the safety profile of the medicinal product, including information on side effects, including side effects that develop when used outside the instructions;
- compliance with the requirements of the legislation on the provision of information on side effects and other safety information to the Agency. In order to perform this function properly and to ensure the quality, integrity and completeness of the information provided, Good validation of signals, as well as the exclusion of duplication of notifications, appropriate standard operating procedures should be developed and applied;
- Ensuring effective interaction with the agency, including information on new risks and changes in medicine safety profile in the main file of the pharmacovigilance system, risk management system, risk minimization measures, periodically updated safety report, corrective and preventive measures, post-registration safety surveys ;
- Ensuring compliance of information on medicines (instructions for use and brief characteristics of medicines) with the level of modern scientific knowledge;
- providing safety information to medical staff and patients.

### **3.7. Ensuring compliance with the requirements of the legislation by the institution**

3.7.1. The organization should have a process quality assurance system to ensure the following:

- assessment of the quality of information provided on pharmacovigilance;
- evaluation and processing of pharmacovigilance data in accordance with the requirements of the current legislation;
- ensuring independence in the implementation of pharmacovigilance activities;
- effective informing of patients, medical staff, license holders and the general public;
- conducting inspections, including pre-registration inspections.

3.7.2. Independence in the implementation of pharmacovigilance activities is determined by the fact that all regulatory decisions are made only in favor of the patient's health and public health.

### **3.8. Document control**

3.8.1. The documentation management system is part of the quality system and covers all documents of the pharmacovigilance system and provides access to information retrieval and follow-up of procedures performed, including new security information evaluation procedures, depending on the time of the assessment and decision-making.

3.8.2. The documentation management system should provide the following:

- quality of pharmacovigilance data, including completeness, accuracy and completeness;
- effective transmission of information inside and outside the enterprise;
- storage of documents related to pharmacovigilance systems and implementation of pharmacovigilance for each medicinal product in accordance with the applicable storage periods.

3.8.3. The license holder must ensure that all pharmacovigilance information is reliably documented, stored and handled in order to accurately disclose, interpret and verify the information. A system for tracking and subsequent evaluation of notification of additional effects by the cardholder should be provided.

3.8.4. The document management system should include comprehensive measures to ensure data security and confidentiality in order to meet the requirements for the protection of patients' personal data in accordance with the requirements of applicable law.

3.8.5. The document management system should include processes to ensure that pharmacovigilance data is protected from loss or destruction.

### **3.9. Quality system documentation**

3.9.1. All elements, requirements and provisions of the quality system must be properly documented and systematized in the form of written guidelines and procedures, such as a quality plan, quality guidance and quality reports.

3.9.2. The quality plan identifies the processes to be applied to achieve the set goals and the main objectives of the quality system. Qualitative procedures in themselves constitute a description of the established procedure for carrying out processes, and standard operating procedures may also have staffing instructions and other forms of guidance. Quality management defines the scope of the quality system, the processes of the quality system and their interrelationships. Quality reports include the results obtained from the operation of the system or the confirmation of the activities carried out.

3.9.3. The quality system must be reflected in the following documents:

- documentation on organizational structure and staff responsibilities;
- training plan and reports on conducted trainings;
- instructions on the appropriateness of the management process;
- instructions on critical processes in pharmacovigilance, including ensuring process continuity;
- performance indicators used for continuous monitoring of the Good implementation of pharmacovigilance functions;
- quality system audit and follow-up audit findings, including information and results obtained.

Also, the quality system documentation should include:

- methods of monitoring the effectiveness of the quality system and, in particular, the ability to perform the tasks of its quality system;

- reports on the results of pharmacovigilance procedures confirming the implementation of all planned stages and activities;
- reports and documents on means and equipment, including qualification and validation activities and functional characteristics verification, confirming that all relevant requirements, protocols and procedures have been met;
- control over deviations from the established quality system, corrective and preventive measures, reports confirming the assessment of the effectiveness of the measures taken.

### **3.10. Additional documentation on the quality system of the license holder**

In addition to the documentation required for the quality system, the licensee must document the hierarchical interaction of management and control personnel, as well as the organizational structure that defines the responsibilities and functions of personnel and the resource management system.

### **3.11. Additional documentation on the quality system of the institution**

In addition to the documentation required for the quality system, the Institution should share the responsibilities and responsibilities of all staff, as well as identify liaison officers who provide liaison between licensees and those who provide information on risks related to medicines.

### **3.12. Critical processes in pharmacovigilance**

3.12.1. Critical processes in pharmacovigilance include:

- continuous monitoring of safety profile and benefit-risk ratio of registered medicines;
- application, implementation and evaluation of the risk management system by assessing the effectiveness of risk minimization measures;
- Procedures for working with ICSR: collection, processing, management, quality control, obtaining missing data, numbering, classification, identification of recurring notifications, evaluation and timely submission;
- identification, investigation and evaluation of signals;
- planning, development (including data evaluation and quality control), submission and evaluation of periodically updated security reports;
- fulfillment of obligations and answering the inquiries of the Institution when required by the Institution, as well as providing accurate and complete information to the Institution;
- ensuring the interaction between pharmacovigilance and the system of quality control of medicines;
- informing the Agency on all changes in the assessment of the benefit-risk ratio of registered medicines;

- informing medical and pharmaceutical workers and patients about all changes in the assessment of the benefit-risk ratio in order to ensure the safe and effective use of medicines;
- ensuring that the information on the medicinal product, including the instructions for use of the medicinal product, is in line with the level of modern scientific and medical knowledge, as well as with the recommendations and assessments of the competent authorities;
- implementation of all required measures in case of change of registration status due to reconsideration of security profile.

### **3.12.2. The process continuity plan should include:**

- identification of events that may have a significant impact on the personnel and infrastructure of the enterprise in general or in part on the structures and processes of pharmacovigilance;
- backup systems in case of urgent exchange of information with other licensees and the Agency with other enterprises sharing the functions of pharmacovigilance within the enterprise.

## **3.13. Monitoring the operation and effectiveness of the pharmacovigilance system and its quality system**

3.13.1. Methods of monitoring the operation and effectiveness of the pharmacovigilance system should include:

- review and analysis by the persons responsible for the management of the system;
- audits;
- verification of compliance with the requirements;
- inspections;
- assessment of the effectiveness of measures taken to minimize risk and ensure safe and effective use of medicines.

3.13.2. For the purpose of monitoring, the indicators that form the basis for assessing the effectiveness of the pharmaceutical control system in terms of quality requirements must be determined in advance.

3.13.3. Audits based on risk assessments of the quality system should be conducted at regular intervals to confirm compliance with established quality requirements and to determine effectiveness. A quality system audit should include an audit of a pharmacovigilance system with an integrated quality system. The audit should be performed by professionals who are not involved in performing the functions and procedures to be audited. Based on the results of each audit of the quality system and subsequent audits, a report should be prepared, which should be evaluated by those responsible for the organization of the relevant audited processes. If necessary, corrective and preventive measures should be taken based on the results of the audit.

3.13.4. The agency must ensure the monitoring of the implementation of pharmacovigilance activities and obligations by licensees established by law. Inspection of licensees by the agency is one of the measures to ensure monitoring.

### **3.14. Person in charge of pharmacovigilance**

3.14.1. The holder of a license in the territory of the Republic of Azerbaijan must appoint a person responsible for pharmacovigilance with the qualities specified in sub-clause 2.1.5 of the Rules. The holder of the card must inform the Agency of the surname and contact information of the person responsible for pharmacovigilance. If this information is changed, the cardholder must inform the Agency in the form and within the period specified in sub-clause 4.1.5 of the Rules.

3.14.2. Each pharmacovigilance system may have only one person responsible for pharmacovigilance. If he is able to perform all his duties, the services of the person in charge of pharmacovigilance may be used by more than one licensee in general or separate pharmacovigilance systems, or this person may perform the functions of the person in charge of pharmacovigilance for more than one pharmacovigilance system. In addition to the person in charge of pharmacovigilance, the Authority has the right to legally require the appointment of a pharmacovigilance coordinator who reports to the person in charge of pharmacovigilance at the national level. At the national level, the coordinator may also act as the person responsible for pharmacovigilance.

3.14.3. The responsibilities of the person in charge of pharmacovigilance should be defined in the job description.

3.14.4. The holder of the license gives sufficient authority to the person in charge of pharmacovigilance to manage the activities of the pharmacovigilance and quality system. The holder of the license gives the person responsible for pharmacovigilance access to the main file of the pharmacovigilance system, as well as powers over it and provides access to information on any changes in the main file of the pharmacovigilance system. The powers of the pharmacovigilance system and the main file of the pharmacovigilance system allow the person in charge of pharmacovigilance to make changes to risk management plans (hereinafter RMP), the system and the development of regulatory measures in response to emergencies to change the safety profile.

3.14.5. The holder of the license provides all the systems and processes that allow the person in charge of pharmacovigilance to fulfill the obligations imposed on him. To this end, the licensee develops mechanisms that can help the person in charge of pharmacovigilance access all important information and, if necessary, all information, for example:

- all other information related to the assessment of the emergency situation and the benefit-risk ratio to change the safety profile of medicines covered by the pharmacovigilance system;

- ongoing and completed clinical trials / trials and other trials / trials known to the licensee that may be related to the safety of the medicinal product;
- information obtained from sources other than the licensee's sources, for example, from sources that have a contract agreement with the licensee;
- Pharmacovigilance procedures developed by the licensee at each level in order to ensure compliance with and compliance with the requirements.

3.14.6. The person in charge of pharmacovigilance receives from the management information on the results of regular inspections of the quality system and the measures taken, information on compliance with the requirements set by the audit of the pharmacovigilance system. The person in charge of pharmacovigilance has the authority to initiate an audit if necessary. Management will provide the pharmacovigilance officer with a copy of the corrective and preventive action plan after each audit to ensure that appropriate corrective action is taken.

3.14.7. The holder of the license provides access to information from the database on additional effects at the disposal of the person in charge of pharmacovigilance.

### **3.15. Qualification of the person responsible for pharmacovigilance**

3.15.1. The person in charge of pharmacovigilance must have theoretical and practical knowledge on the implementation of pharmacovigilance activities. The person in charge of pharmacovigilance must have the skills or access to such examinations in the management of pharmacovigilance systems, as well as in the fields of medicine, pharmaceutical sciences, as well as epidemiology and biostatistics.

3.15.2. Prior to the appointment of the responsible person, the license holder shall ensure that the person responsible for pharmacovigilance is trained in the field of his / her pharmacovigilance system. The training and its results must be reliably documented.

### **3.16. Functions of the person responsible for pharmacovigilance**

3.16.1. A qualified person authorized for pharmacovigilance in the territory of the Republic of Azerbaijan is an individual.

3.16.2. The person in charge of pharmacovigilance appointed by the licensee must have the appropriate qualifications (see: 3.15.) And must always be at the disposal of the licensee. The person in charge of pharmacovigilance is responsible for the establishment and operation of the pharmacovigilance system by the licensee and thus has sufficient authority to influence the implementation of the quality control system of the pharmacovigilance and pharmacovigilance system, support, comply with and increase compliance. For this reason, the person in charge of pharmacovigilance should have the authority and responsibility to ensure compliance with the requirements of the legislation and to increase the level of compliance with the main file of the pharmacovigilance system.

3.16.3. The person in charge of pharmacovigilance in connection with medicines covered by the pharmacovigilance system of the license holder has the following obligations:

- to review the safety profiles of medicines and emergencies related to changes in safety profiles;
- to have complete information on the conditions and obligations set at the time of issuance of registration cards, as well as other obligations related to the safety or safe use of medicines;
- have complete information on risk mitigation measures;
- to participate in the review and approval of post-registration security research protocols;
- have complete information on post-registration security surveys designated by the competent authority, including the results of such surveys;
- Make additions to the RMP;
- to ensure the implementation of pharmacovigilance functions in accordance with the requirements of the legislation and the submission of all documents related to pharmacovigilance;
- to ensure the necessary quality of pharmacovigilance information submitted to the competent authority, including accuracy and completeness;
- To provide complete and timely answers to all requests of the organization to provide additional information necessary for the assessment of the benefits and risks of the medicine;
- to submit to the Organization any information related to the assessment of the risk-benefit ratio;
- assist in the development of regular safety response measures (for example, changes in medical guidelines, emergency restrictions and the dissemination of information to patients and health care providers);
- Act as a single pharmacovigilance coordinator in relation to the organization, as well as a coordinating person for pharmacovigilance inspections with 24-hour access.

3.16.4. The person in charge of pharmacovigilance must comply with all aspects of the pharmacovigilance system, including its quality system (eg, standard operating procedures, contract agreements, database operations, compliance with quality system requirements, complete and timely submission of information, submits periodically updated safety reports and audit finding, monitors pharmacovigilance training). The person in charge of pharmacovigilance must have information on the validation status of the database on side effects against medicines, as well as on the deficiencies identified during the validation process and the corrective measures taken. The pharmacovigilance officer must also be aware of all significant changes made to the database (for example, changes that may affect pharmacovigilance activities).

Under his supervision, the person in charge of pharmacovigilance may delegate the authority to perform specific tasks to qualified and trained persons, for example, as an expert on the safety of certain medicines, provided that the control system oversees the function of the safety profile of the entire system and all medicines. implementation of activities. Such transfer of authority over the functions performed must be reliably documented.

### **3.17. Specific processes of the quality system of license holders**

3.17.1. The license holder develops additional special processes for the following purposes:

- submission of information on additional effects to the national database of the Institution within the period required by the legislation;
- storage of important documents describing the pharmacovigilance system during the existence of the system described in the main file of the pharmacovigilance system and for at least 5 years after its termination;
- storage of information and documents on pharmacovigilance of the medicinal product for at least 10 years after the expiration of the state registration of the medicinal product;
- Update information on medicines in accordance with modern scientific knowledge, including safety profile and benefit-risk assessment, as well as recommendations posted on the web portal of the competent authority.

For this purpose, the licensee regularly checks the web portal of the competent authority for the presence of relevant changes in the assessment of safety profile and risk-benefit ratio, as well as changes in medical recommendations and other regulatory measures.

3.17.2. During the storage of the documents, the cardholders ensure that the documents can be restored.

3.17.3. Documents may be stored in electronic format provided that the electronic system is reliably validated and there are agreements on the protection of this system, access to the system and storage of data backups. In the case of transferring documents from paper to electronic format, the transfer process must ensure that all information is stored in the original format, in a readable form, and that the means used for storage are readable throughout the retention period.

3.17.4. In case of misappropriation of the cardholder's business by another enterprise, all documents must be transferred and kept in full.

### **3.18. Requirements for the quality system when delegating the functions of pharmacovigilance by the licensee**

3.18.1. The holder of the license may delegate the authority to perform pharmacovigilance tasks in whole or in part, as well as the authority to perform the functions of the person responsible for pharmacovigilance to another organization or person (if such a person may be subject to the same requirements as the

enterprise). In this case, the licensee is always responsible for the fulfillment of pharmacovigilance tasks and obligations, quality assurance and completeness of the pharmacovigilance system.

3.18.2. When the license holder transfers authority on specific tasks to another organization, the license holder is responsible for the application of an effective quality system for the implementation of the assigned tasks. The requirements for a pharmacovigilance system defined in accordance with Good Pharmacovigilance Practice (hereinafter the Guidelines) also apply to other organizations.

3.18.3. When delegating the execution of assignments to another organization, the licensee shall ensure that the agreements with other relevant organizations are documented with a detailed, accurate and constantly updated description of the assignments and the obligations of each party. A description of the activity and / or service to which the executive authority has been transferred must be included in the main file of the pharmacovigilance system. An inspection may be carried out by another organization at the discretion of the competent authority.

3.18.4. In order to monitor the implementation of the agreements on the pharmacovigilance agreement, it is recommended that the licensee conduct regular audits of the organizations to which the authority to perform pharmacovigilance functions is delegated.

### **3.19. General obligations of the Pharmacovigilance Agency**

3.19.1. The agency is responsible for the implementation of pharmacovigilance tasks assigned to it in accordance with the relevant national legislation. To this end, the Agency ensures the functioning of the pharmacovigilance system, creates and implements a Good, effective quality system of pharmacovigilance activities.

3.19.2. The agency cooperates with the competent authorities of other countries to continuously improve pharmacovigilance systems to achieve high standards of public health, including the use of combined international resources to optimize the use of existing resource base.

### **3.20. Functions of the organization**

3.20.1. The agency must apply and ensure the effective operation of the pharmacovigilance system during the implementation of its tasks and participation in pharmacovigilance activities in the country. In this context, the Agency is responsible for monitoring the safety of each medicinal product registered in the territory of the Republic of Azerbaijan.

3.20.2. The tasks and responsibilities of the authorized body for pharmacovigilance include cooperation in the identification of signals and the application of risk minimization measures in the adoption of relevant decisions.

3.20.3. The agency is responsible for inspecting the implementation of pharmacovigilance of medicines in its territory by applicants / manufacturers of

medicines, as well as for conducting inspections of pharmacovigilance systems of licensees.

### **3.21. Planning preparedness for pharmacovigilance in health emergencies**

The pharmacovigilance system of license holders and the Institution must be adapted to health emergencies. If necessary, preparation plans should be developed.

A health emergency is in itself a threat to public health recognized by the World Health Organization or the Organization.

Pharmacovigilance requirements for emergencies in public health are determined by the Agency. Inform pharmacists and the public about pharmacovigilance requirements. The agency publishes emergency notices on its website.

## **4. The main file of the pharmacovigilance system (MFPS)**

### **4.1. Structures and processes**

4.1.1. The main file of the pharmacovigilance system (hereinafter - MFPS) is intended for the description of the pharmacovigilance system and documented confirmation of its compliance with the requirements of the legislation. The MFPS allows licensees to reliably plan and audit the pharmacovigilance system, as well as to be inspected by the Agency. The MFPS contains an overview of the licensee's pharmacovigilance system, which allows for a general assessment by the Institution at the registration and post-registration stages.

4.1.2. The compilation and maintenance of the information contained in the MFPS provides the licensee and the person in charge of pharmacovigilance with the following opportunities:

- to make sure that the pharmacovigilance system is applied in accordance with the requirements of the legislation;
- to confirm the compliance of the system with the requirements in force;
- to obtain information on system shortcomings or to identify cases of non-compliance;
- to obtain information on the ineffectiveness or risks of certain areas of pharmacovigilance activities.

4.1.3. The use of information in the MFPS helps to optimize the process of Good management of the system, as well as to improve the pharmacovigilance system. The requirements for the issuer to provide a summary of the pharmacovigilance system in the form of a MFPS, as well as the chronology of changes made by the Authority, facilitate the planning and effective conduct of inspections by the Authority based on the risk assessment method.

### **4.2. MFPS registration and support**

4.2.1. Summary of the licensee's pharmacovigilance system

When applying for state registration of a medicinal product, the holder of the license shall provide a brief summary of the pharmacovigilance system. The summary of the pharmacovigilance system is as follows:

- a document on the appointment of the license holder as a person responsible for pharmacovigilance;
- contact information of the person responsible for pharmacovigilance (address, telephone, fax, e-mail, etc.);
- a certificate signed and stamped confirming that the license holder has the equipment required to perform his duties and responsibilities related to pharmacovigilance;
- certificate signed and stamped on the existence of the main file of the pharmacovigilance system of the medicinal product;

#### **4.2.2. The address of the MFPS**

MFPS must be kept in the territory of the Republic of Azerbaijan or in the place where the main activity on pharmacovigilance is carried out, or in the place where a qualified person is responsible for the implementation of pharmacovigilance, regardless of the format (paper or electronic). The agency must be informed of the address of the MFPS, as well as immediately notified of any changes in its address. The information required at the address of the MFPS includes the physical address of the licensee's office or the office of the third party under the contract. This address may be different from the address of the applicant / holder, for example, if the holder has another office or if the main activity is performed by a third party under the contract. When determining the main place of operation of the pharmacovigilance activity, the licensee must take into account the more important address for the pharmacovigilance system as a whole. The holder of the card must have a relevant justification for the decision to locate the MFPS. If the main activity is carried out outside the Republic of Azerbaijan or the main location cannot be determined, the standard address of the MFPS is the place where the activity of the person responsible for pharmacovigilance is carried out.

#### **4.2.3. Transfer of MFPS obligations**

4.2.3.1. The transfer or assignment of obligations and activities under the MFPS must be documented and verified by the holder of the certificate in order to confirm the fulfillment of its obligations. In order for the pharmacovigilance officer to make changes to improve the system, he or she must be informed of the changes in the MFPS in order to exercise his or her powers. The types of changes that must be immediately notified to the person in charge of pharmacovigilance are:

- Changes to be notified to the MFPS or its address;
- Addition of corrective and / or preventive measures to the MFPS (for example, based on the results of audits and inspections) and management of deviations from

the processes specified in the quality management system of the pharmacovigilance system;

- changes in the information contained in the MFPS that meets the Good control criteria (within the scope, functionality and compliance of the system);

- Amendments to the agreement on the submission of the MFPS to the Agency.

4.2.3.2. The person in charge of pharmacovigilance must confirm in writing that he has been notified of the following changes:

- inclusion of medicines in the pharmacovigilance system for which the person responsible for pharmacovigilance is responsible;

- transfer of responsibilities under the pharmacovigilance system to the person responsible for pharmacovigilance.

### **4.3. Description of pharmacovigilance systems**

The MFPS should describe the pharmacovigilance system of the licensee in relation to one or more medicines. The licensee may apply different pharmacovigilance systems for different categories of medicines. Each such system must be described in different MFPSs. The main files submitted must cover all medicines licensed for the state registration of the licensee.

4.3.1. If the licensee has more than one pharmacovigilance system, for example, specific pharmacovigilance systems for certain types of medicines (vaccines, sanitary products, etc.) or if the pharmacovigilance system covers more than one licensee's medicines, which describes each system a MFPS is submitted.

4.3.2. The holder of the certificate must appoint a person responsible for pharmacovigilance responsible for the establishment and application of the pharmacovigilance system described in the MFPS.

4.3.3. When a pharmacovigilance system is used by more than one licensee, each licensee is responsible for the existence of the MFPS, which describes the pharmacovigilance system of the product. The holder of the license may, on the basis of a written agreement, delegate in whole or in part the executive powers of the pharmacovigilance activity for which it is responsible for Good performance. In this case, the licensee's MFPS may contain, in whole or in part, a cross-reference to the MFPS, which is governed by the system of the other party to whom the authority to perform activities is transferred by the licensees and the competent authorities. The holder of the license must ensure the conformity of the content of the reference document (s) to the pharmacovigilance system applied to the medicine (s).

4.3.4. Where appropriate, a list of all MFPSs supported by one licensee is provided in the appendix. The attached information includes information on the location of the main file (s), information on the person (s) responsible for pharmacovigilance and the relevant medicinal product (s).

4.3.5. The summary submitted to the agency should not include several addresses of the MFPS.

4.3.6. During the transfer of executive power over the pharmacovigilance system and its main file, the licensee bears full responsibility for the pharmacovigilance system, the provision of information on the address of the MFPS, the conduct of the MFPS and its submission to the Agency upon request. There should be written agreements on the submission and support of the MFPS, as well as a description of the functions and obligations for the implementation of pharmacovigilance in accordance with the requirements of the legislation.

4.3.7. If the pharmacovigilance system is used by more than one licensee, it is recommended that the partners coordinate the joint management of the relevant sections of the system within the framework of personal key files. The accessibility of the MFPS for all relevant cardholders must be specified in the written agreements on its submission to the competent authorities. It is important for the licensee to make sure that the pharmacovigilance system covering his products meets all relevant requirements.

#### **4.4. Information that must be provided in the MFPS**

The MFPS must contain relevant documents describing the pharmacovigilance system. The content of the main file of the pharmacovigilance system should reflect the global accessibility of information on the safety of medicines registered in the territory of the Republic of Azerbaijan. The document should have content and headings to allow for quick navigation.

##### 4.4.1. Section of the main file on the person responsible for pharmacovigilance

The main file should contain information about the person responsible for pharmacovigilance:

- a description of the obligations that ensure that the person responsible for pharmacovigilance has the appropriate authority over the pharmacovigilance system in order to ensure, maintain and enhance compliance with the requirements;
- work experience containing basic information about the person responsible for pharmacovigilance;
- contact information of the person responsible for pharmacovigilance. The contact information provided must include the name, surname, patronymic, postal address, telephone and fax numbers, e-mail and work address of the responsible person;
- information on the implementation of the powers of the person replacing him in the absence of the person responsible for pharmacovigilance. In case of transfer of executive powers of the specific instructions of the person in charge of pharmacovigilance to another executor, the list of assignments to which the executive authority has been delegated, a description of the activity to which the executive authority has been transferred and the person to whom it has been delegated shall be attached.
- a description of the qualifications and experience of the person responsible for pharmacovigilance activities related to pharmacovigilance activities.

##### 4.4.2. Section of the main file on the organizational structure of the license holder

4.4.2.1. A description of the organizational structure of the relevant pharmacovigilance system of the license holder must be submitted. The description should provide a clear picture of the relationship between the company (s) involved, the main departments of pharmacovigilance and the organizations and structural units involved in the implementation of pharmacovigilance activities. The following information must be provided in the main file of the pharmacovigilance system:

- organizational structure of the license holder, indicating the position of the person responsible for pharmacovigilance;
- pharmacovigilance activities, including the collection and evaluation of MFPS, the inclusion of notifications in the security database, the preparation of periodically updated security reports, the detection and analysis of signals, the management of MFPS, the implementation of pre-registration and post-registration research / testing the place (s) where the activities are carried out to manage changes in the information on the management and safety of the medicinal product.

#### 4.4.2.2. Transfer of executive powers

4.4.2.2.1. Where appropriate, the MFPS should include a description of the activities for which the executive authority has been transferred and / or the performance of its pharmacovigilance obligations.

4.4.2.2.2. The information in the section should include confirmation of interaction with other organizational structures, such as a joint marketing agreement and the involvement of contractors in pharmacovigilance activities. Such a description may be in the form of a list / table: the parties involved, the commitments made, the relevant medication (s) and the areas. Types of organizations that provide schedule services (eg, medical information, auditors, patient support providers, research data processing), commercial agreements (distributors, license partners, joint marketing, etc.) and other technical providers (hosting computer systems on providers' servers) etc.) should be compiled accordingly. Individual agreements under the contract are submitted at the request of the Institution or during the inspection and audit, a list of which is specified in the annexes.

4.4.2.2.3. The MFPS should include copies of agreements signed on the transfer of executive powers of significant activities as follows:

- pharmacovigilance services (person in charge of pharmacovigilance, input of safety information, preparation of periodically updated safety reports, electronic submission of MFPS, assessment of safety information, etc.);
- Transfer of executive powers on MFPS activities.

#### 4.4.3. The section of the main file on the sources of access to security information

4.4.3.1. The description of the main sections of safety information should include all parties responsible for the collection of all notifications obtained on request and spontaneous notifications of side effects against medicines registered in the territory of the Republic of Azerbaijan. This should include the location of medical information as well as subsidiary offices. This information may be in the form of a

list indicating the country, nature of the activity and the medicine (s) (depending on the type of medicine given). Information on third parties (licensed partners or local distributors / marketing agreements) should also be included in the section describing the agreement and arrangements.

4.4.3.2. Sources of security information should also include a current list of research / tests, registers, support or monitoring programs sponsored by the licensee. The list should describe the status of each research / program globally, the country (s), the medicine (s), and the main objectives. Interventional and non-interventional studies / trials should be indicated separately according to the active ingredients of the medicine. The list should include all studies / programs, ongoing research / programs, as well as studies / programs completed in the last two years.

4.4.4. Section on computer systems and database of the main file

4.4.4.1. The MFPS should describe the responsibilities for the location, functionality, and operation of the database and computer systems used to obtain, verify, present, and assess the security of the information.

4.4.4.2. If several computer systems / databases are used, their application to pharmacovigilance activities should be described in a way that the scope of computerization within the pharmacovigilance system is understandable. The validation status of key aspects of the computer system's functionality should also be described; as well as backup procedures and electronic data archives, test structure, control changes, description of existing documentation, which are important for compliance with pharmacovigilance requirements. The paper format (when the electronic system is used only for emergency submission of MFPS) should describe the mechanisms used to manage the data, as well as to ensure access to and completeness of the data.

#### **4.4.5. Processes section of the main file**

4.4.5.1. An important component of any pharmacovigilance system is the availability of standard written procedures at the site of the activity. Section 3 of this Instruction describes the minimum written procedure required for pharmacovigilance. Documentation of existing procedures in the MFPS (references to specific standard operating procedures, guidelines, etc.), types of data (for example, types of MFPS information) and instructions on how to keep records (eg security database, paper at the point of acquisition) files) should be described.

4.4.5.2. The FSA should include a description of the data processing and registration processes involved in carrying out pharmacovigilance activities, which should include the following aspects:

- continuous monitoring of the benefit-risk ratio of the medicinal product, the results of the assessment and the decision-making process on appropriate measures; signal generation, verification and evaluation process; obtaining security access information from the database, exchanging information with clinical departments, etc .;

- monitoring of the risk management system (s) and the results of the application of risk minimization measures; in case of involvement of several departments in this process, the rules of their interaction are determined by written procedures or agreements;
- collection, verification, acquisition of subsequent information, evaluation and submission of information on MFPS; (Procedures for this section should clearly distinguish between local and international activities.)
- preparation and submission of periodically updated security reports;
- providing information on safety issues to consumers, health workers and authorities;
- make changes to safety in the instructions for use of the medicine and information for patients; (Procedures should include internal and external information exchange.)

4.4.5.3. The holder of a license for each area of activity must be ready to provide timely approval of the functioning of the decision-making and action system.

4.4.5.4. The pharmacovigilance system should provide information on the function of other activities that confirm the existence of a Good quality assurance system. In particular, the functions and responsibilities of the person in charge of pharmacovigilance, responding to inquiries from the competent authorities for information, literature search, monitoring changes in the security database, agreement on the exchange of security information, archiving security information, audit of pharmacovigilance, quality control and training is related. During the inspection, a table (name and number) containing all the procedural documents of the pharmacovigilance can be used.

4.4.6. Section on the application of the pharmacovigilance system in the MFPS

The MFPS should include confirmation of continuous monitoring of the functioning of the pharmacovigilance system, as well as verification of key outcomes. The MFPS should include a description of the monitoring method and at least the following:

- A description of the procedure for assessing the accuracy of the submission of MFPS. Illustrations / graphs confirming the timely submission of information in accordance with the requirements of applicable law;
- a description of the information provided and the control indicators used to check the quality of pharmacovigilance activities. This includes information obtained from the competent authorities regarding the quality of submission of additional impact notices, periodically updated safety reports and other information provided;
- an analysis of the timeliness of the submission of periodically updated security reports to the Institution (the latest information used by the licensee to assess compliance should be included);
- an analysis of the timeliness of security changes compared to the deadlines set, as well as the date and description of the necessary security changes identified but not submitted;

- analysis of the fulfillment of RMP obligations or other obligations and requirements related to pharmacovigilance, if appropriate;
- a list of pharmacovigilance performance indicators, if applicable.

The purpose of the pharmacovigilance system should be described and explained. A list of performance indicators should be included in the appendix to the MFPS.

#### 4.4.7. MFPS quality system section

This section describes the quality management system within the structure of the organization and the application of the quality system in pharmacovigilance. These include:

##### a) Procedure documents

A list of documented procedures related to pharmacovigilance activities, indicating their interactions with other approaches and functions for evaluating procedures. The list should include the document number, name, effective date (for all standard operating procedures, operating instructions, guidelines, etc.) and a description of the availability of the documents. Standard operating procedures for service providers and other third parties should be specified.

##### b) Training

A description of resource management during pharmacovigilance activities is provided:

- references to the organizational structure, including qualification documents, indicating the number of people involved in the implementation of pharmacovigilance activities;
- list of staff location;
- a brief description of the training content, including references to the training documents;
- list of instructions on critical processes, indicating the necessary information on the documents.

Personnel must be properly trained to carry out pharmacovigilance activities. This applies not only to the staff of pharmaceutical control departments, but also to other persons who may receive safety notices.

##### c) Audit

Information on the audit of the quality assurance system of the pharmacovigilance system should be included in the MFPS. The appendix should include a description of the planning methods and reporting mechanisms of the pharmacovigilance system, as well as a valid list of planned and completed audits of the pharmacovigilance system. This list should include the date (s), scope and status of audits by service providers, specific types of pharmacovigilance activities or locations of pharmacovigilance activities, as well as the areas of interaction related to the performance of the obligations.

The MFPS should also include comments on audits that yield significant results during the course. This means that a short description of the results of the assessment, which is assessed as significant or critical, as well as the corrective and

preventive action plan, with deadlines, should be included in the list of audits conducted. Reference should be made to the complete audit finding and the document (s) containing the corrective and preventive action plan. Comments, corrective and preventive measures, as well as instructions on the audit finding, should be included in the main file of the pharmacovigilance system until the corrective and / or preventive measures are fully implemented, ie comments should be made only after the results of corrective measures are demonstrated. and / or are revoked upon confirmation of significant improvement of the system or after approval by an independent person.

As a means of managing the pharmaceutical control system, as well as providing a basis for audits and audits, the MFPS should also include a description of the processes for recording, processing and eliminating deviations found in the quality management system.

#### 4.4.8. In addition to the MFPS

In addition to the MFPS, it must contain the following documents:

a) The list of medicines covered by the MFPS, including the name of the medicine, the international non-proprietary name (s) of the active substance (s) (BPA) and the state registration certificate, registered by the card holder in the territory of the Republic of Azerbaijan and other countries. name of the country of residence, number (s) of the state registration certificate (s);

The list should be based on the active ingredients and, where appropriate, indicate the existence of specific requirements for the safety of the medicinal product (for example, the risk mitigation measures described in the RMP).

In the case of joint pharmacovigilance systems, the list of license holders and medicines applying the pharmacovigilance system described in the MFPS should be included in such a way that a complete list of medicines covered by the main file of the pharmacovigilance system is available.

b) A list of contract agreements relating to delegated pharmacovigilance activities, including the relevant medicines and the territory (s);

c) a list of assignments delegated by the person in charge of pharmacovigilance;

d) Lists of all audits completed and planned audits completed during the decade;

e) List of pharmacovigilance performance indicators, where appropriate;

f) A list of other MFPSs maintained by the licensee, if applicable.

### **4.5. Change control, versions and archiving**

4.5.1. The agency may request information on important changes in the pharmacovigilance system that may include, but are not limited to:

- changes in the database on the security of the pharmacovigilance system, changes in the validity status of the database, as well as changes in the information on the transmitted or transferred data, which may include changes in the database itself or in interconnected databases;

- changes in the provision of significant pharmacovigilance services, in particular in relation to agreements on important contracts for the provision of safety information;

- organizational changes, such as the acquisition of one company by another, its merger with another company, the relocation of pharmacovigilance activities or the transfer of authority to manage the MFPS.

4.5.2. Because the MFPS can contain periodically variable lists of medicines and activities, licensees should implement a change monitoring system and develop Good methods of keeping the MFPS informed of relevant changes on a regular basis for a Good review. In addition, changes to the MFPS must be recorded in such a way that there is a permanent history of these changes (indicating the date and content of the change). Constantly updated information, such as medicine lists and standard operating procedures or compliance information, can be recorded through a history of changes that may include information on controlled systems (eg, electronic data management system or regulatory database). Thus, it is possible to manage replaced versions of documents outside the content of the text of the MFPS, provided that the history of changes is taken into account and submitted to the Agency upon request. Significant or significant descriptive changes in the textual content of the main file may require the creation of a new version of the MFPS.

4.5.3. Licensees should develop documentation control procedures and justify the chosen method in order to reliably manage the FSED support process. The basic principle is that the MFPS provides a current description of the pharmacovigilance system as a basis for inspections and audits, but an assessment of the function and direction of the pharmacovigilance system at earlier stages may require additional familiarity with the system.

4.5.4. Amendments to the FSA should also take into account joint pharmacovigilance systems and activities to which delegated executive powers for pharmacovigilance have been delegated. Good control of changes involves the registration of the content and date of notifications of changes by the Agency, the person in charge of pharmacovigilance and third parties.

4.5.5. The MFPS must be legible and accessible. It is necessary to provide a description of the archiving procedure on MFPS print and / or electronic format media.

#### **4.6. Submission of MFPS**

The person in charge of pharmacovigilance must have constant access to the MFPS. Upon request, the Authority must have permanent access to the MFPS. The information in the MFPS should be detailed, accurate and reflect the current pharmacovigilance system, which means that the information in the MFPS must be updated and, if necessary, reviewed, taking into account the experience gained, scientific and technical developments and changes in legislation. expresses. Access

to the MFPS must be provided by the holder of the card within 7 working days after receipt of the relevant request.

#### 4.6.1. Format and structure

The MFPS is provided in electronic format at the request of the Agency, subject to the submission of a clearly structured print copy. In any format, the FSA must be in a readable, complete and accessible form to ensure that all documents can be evaluated and tracked. Restricting access to the FSA may be required in order to exercise Good control over its content and to distribute certain responsibilities for the management of the MFPS (in the context of monitoring and archiving changes).

### **4.7. Liabilities**

#### 4.7.1. License holders

4.7.1.1. Licensors should develop and implement a pharmacovigilance system to control and monitor one or more medicines. They are also responsible for establishing and supporting the FSA, which registers pharmacovigilance activities related to one or more registered medicines. The holder of the license must appoint a person in charge of pharmacovigilance, who is responsible for the establishment and functioning of the pharmacovigilance system described in the MFPS.

4.7.1.2. When submitting an application for state registration, the applicant must have a description of the pharmacovigilance system that will operate in the area where the medicine is registered. During the evaluation of the application for state registration, the applicant may be required to submit a copy of the MFPS for review.

4.7.1.3. The holder of the card is responsible for the establishment of the MFPS in the territory of the Republic of Azerbaijan and for the registration of the location of the MFPS in the Institution when applying for state registration. The MFPS should describe the current pharmacovigilance system in the area where the application is submitted for the current time. Information about future components of the system may be included, but these components should be shown as planned, not as current or current.

4.7.1.4. The work of establishing, supporting and submitting the MFPS to the Institution may be delegated to a third party, but the holder bears full responsibility for compliance with the law. Maintenance of the main file of the pharmacovigilance system at a usable and accessible level (permanent access for audit and inspection) may be entrusted to another third party, but the licensee bears the main responsibility for ensuring that this function meets the requirements of the law.

4.7.1.5. In the event of a change in the contact information of the person in charge of pharmacovigilance or contact information, as well as the address of the MFPS, the licensee shall submit an application to the Agency for appropriate changes.

Licensees are also responsible for updating information on the address of the person in charge of pharmacovigilance and the MFPS.

#### 4.7.2. Institution

4.7.2.1. The agency is responsible for overseeing the pharmacovigilance systems of licensees. The full MFPS may be required at any time, for example, when there are questions about the pharmacovigilance system and / or the safety profile of a medicine, or in preparation for an inspection. A summary of the pharmacovigilance system or information on changes in the content of the FSA is also used in planning and conducting inspections.

4.7.2.2. The agency may exchange information on pharmacovigilance systems with other competent authorities and use that information to inform national inspection programs based on risk assessment.

#### 4.8. Access to MFPS

4.8.1. The MFPS is maintained at a level suitable and accessible to the person in charge of pharmacovigilance. It must also be accessible for inspection, whether or not the notice has been given in advance.

4.8.2. The holder of the card supports the MFPS and provides a copy upon request. The holder of the card shall submit a copy of the MFPS within 7 working days after receiving the request from the Agency. MFPS is available in easily readable electronic format or in a clearly structured paper format.

4.8.3. When the same MFPS is used by more than one licensee (using a common pharmacovigilance system), the relevant MFPS for each of them must be available in such a way that each licensee will be able to submit the MFPS to the Authority within 7 working days after receiving the request.

4.8.4. As a rule, MFPS is not required for state registration during the evaluation of new applications (ie before the state registration of the medicine), but in special cases, especially when applying a new pharmacovigilance system or when a medicine safety problem is detected, or compliance with pharmacovigilance legislation. may be required when questions arise.

## **5. Inspection of pharmacovigilance system**

### **5.1. Application**

5.1.1. In order to confirm the compliance of license holders with the requirements for pharmacovigilance and fulfillment of obligations, the Agency shall carry out pharmacovigilance inspections of licensees or other organizations involved by the licensee to fulfill pharmacovigilance obligations.

Pharmacovigilance inspections are carried out by inspectors authorized by the Authority to inspect the MFPS materials and documents of the licensee or other organizations involved in the implementation of pharmacovigilance obligations, as well as to inspect their areas. At the request of the agency, the license holders are obliged to provide the MFPS, which will be used to inform about the inspection.

5.1.2. The objectives of pharmacovigilance inspections include:

- confirmation that the license holder has the required personnel, systems, as well as areas, means and equipment to fulfill its pharmacovigilance obligations;
- identification, assessment, registration of non-conformities that may pose a threat to public health and informing the inspected party;
- if necessary, use the inspection results as a basis for the implementation of mandatory measures for the license holder.

5.1.3. The organization has the right to conduct pharmacovigilance inspections before the registration of medicines in order to verify the compliance of the licensee's pharmacovigilance system with the requirements of the legislation and Good pharmacovigilance practices. In particular, the agency may liaise with other competent authorities to exchange information on planned inspections and the results of existing inspections.

5.1.4. Pharmacovigilance programs include scheduled inspections based on a risk-based approach, as well as unscheduled inspections to assess potential inconsistencies or potential risks that may affect the performance of pharmacovigilance functions in relation to a particular medicinal product.

5.1.5. The results of the inspections must be submitted to the subject of the inspection, so that they have the opportunity to comment on the identified violations of the law. The licensee is obliged to eliminate the identified discrepancies in a timely manner by developing and implementing a plan of corrective and preventive measures.

5.1.6. If, as a result of the inspection, it is determined that the license holder has not complied with the pharmacovigilance obligations, the Authority shall, if necessary, take effective, proportionate and restrictive measures to ensure the fulfillment of the pharmacovigilance obligations by the licensee.

## **5.2. Structures and processes**

### 5.2.1. Types of inspections

5.2.1.1. Inspections of the pharmacovigilance system as a whole and for individual medicines

5.2.1.1.1. Inspections within the pharmacovigilance system are aimed at evaluating and analyzing existing procedures, systems, personnel, areas and equipment, as well as determining their compliance with pharmacovigilance obligations established in accordance with the requirements of the legislation. Specific samples of medicines may be used to demonstrate and verify the operation of the pharmacovigilance system during this analysis.

5.2.1.1.2. Inspections aimed at assessing the performance of pharmacovigilance functions in relation to a particular medicinal product are aimed at evaluating and analyzing measures and documentation related to a particular medicinal product. Specific aspects of the general pharmacovigilance system used in the performance of functions related to the inspected medicinal product may also be assessed in the context of the pharmaceutical inspection related to the medicinal product.

## 5.2.1.2. Scheduled and unscheduled inspections on pharmacovigilance

5.2.1.2.1. Scheduled inspections on pharmacovigilance are carried out in accordance with pre-designed inspection programs. To optimize the planning of measures to verify the functioning of the pharmacovigilance system, it is recommended to use an approach based on the assessment of potential risks associated with non-compliance. Scheduled inspections are usually systematic inspections, but one or more specific medicines may be selected as a sample to verify the functionality of the pharmacovigilance system and to obtain practical evidence of its effectiveness and compliance. A standard inspection program may include, for example, an assessment of the state of the system for specific problems identified by experts.

5.2.1.2.2. Unscheduled inspections of the pharmacovigilance system are carried out in case of identification of the initial factor (problem in the system), and in this case, the inspection is considered to be the most optimal method of investigation and assessment of the identified problem. Unscheduled inspections are aimed at assessing specific processes of pharmacovigilance or include the study of identified problems (issues) and their impact on a particular medicine. In specific cases, inspections may be carried out, including a full assessment of the pharmacovigilance system, based on the identified starting factor. Unscheduled inspections are performed if one or more of the initial factors listed below are identified:

1) in connection with the benefit-risk ratio of the medicine:

- if there is a need for further assessment of the system through an audit in the event of a change in the benefit-risk ratio;
- delay or unreliability of the risk identification procedure or unGood notification of changes in the benefit-risk ratio or non-performance of this procedure;
- provision of information on pharmacovigilance problems to the mass media without prior or simultaneous notification of the Agency;
- non-fulfillment of obligations on ensuring the safety of medicines or non-compliance with the requirements of the legislation established by the Agency during the monitoring of pharmacovigilance activities;
- Suspension or withdrawal of a medicine without prior notification of the institution;

2) in connection with the obligation to provide information (urgent and periodic):

- delays or omissions in the provision of security information in accordance with the requirements of applicable law;
- poor quality or incomplete information provided;
- inconsistency between the information provided and other information sources;

3) In connection with the inquiries of the institution:

- refusal to provide the required information or data within the period specified by the Institution;

- Inadequate submission of information on requests for information by the institution or poor quality of this information;

4) in connection with the fulfillment of obligations:

- Concerns about the fulfillment or status of obligations under the RMP;
- delay or non-fulfillment of specific obligations related to monitoring the safety of medicines identified during the issuance of the state registration certificate;
- low quality of reports required as specific obligations;

5) in connection with inspections:

- delays in the application of corrective and preventive measures or unGood implementation of the application;
- ensuring the safety of the medicine obtained during the implementation of other types of inspections in accordance with the requirements of the legislation or the requirements of Good Clinical Practice (GCP), Good Production Practice (GMP), Good Laboratory Practice (GLP) and Good Distributor Practice (GDP) information on non-compliance;
- verification of information obtained from other competent authorities, which may affect the inconsistency of the system;

6) other:

- Problems identified during the review of the MFPS;
- other sources of information or complaints.

#### 5.2.1.3. Pre-registration inspections

5.2.1.3.1. Pre-registration inspections of the pharmacovigilance system are carried out prior to the issuance of the registration card. The purpose of these inspections is to examine the existing or planned pharmacovigilance system based on the system description provided by the applicant. Pre-registration inspections are not mandatory, but may be required in specific situations. The principles of the pre-registration inspection requirement must be pre-determined and must not lead to unreasonable inspections that may delay the issuance of a state registration certificate. The following factors should be taken into account when reviewing the feasibility and justification of pre-registration inspections:

- 1) the applicant has not previously worked with the existing pharmacovigilance system in the territory of the Republic of Azerbaijan or is in the process of creating a new pharmacovigilance system;
- 2) availability of information on the certificate holder's unsatisfactory performance in connection with the requirements of the pharmacovigilance system (for example, history of previous inspections or information / notification on non-compliance obtained from other competent authorities). If a license holder's pharmacovigilance system has previously been found to be severely and / or permanently non-compliant with the applicable requirements, a pre-registration inspection of the pharmacovigilance system may be one of the mechanisms to verify that the pharmacovigilance system has been properly adjusted / improved.

3) in connection with specific problems related to the safety of certain medicines, it may be necessary for the license holder to assess the possibility of the following:

- implementation of risk minimization measures related to specific medicines;
- Good fulfillment of special requirements that can be established to ensure the safety of the use of medicines;
- Good implementation of procedures within the framework of routine pharmacovigilance of a hazardous medicine in connection with the safety profile.

The decision to conduct a pre-registration inspection involves a risk assessment with a comprehensive assessment of specific medicines and system-related issues.

5.2.1.3.2. If the pre-registration inspection of the pharmacovigilance system raises concerns about the licensee's ability to meet the requirements of the pharmacovigilance system established by law and Good pharmacovigilance practice, the competent authority may recommend the following measures:

- refusal to issue a state registration certificate;
- re-inspection prior to the issuance of the state registration certificate in order to confirm that critical non-conformities have been eliminated and the recommendations have been followed;
- issuance of a certificate of state registration with the recommendation to inspect the pharmacovigilance system at an early stage after registration.

#### 5.2.1.4. Post-registration inspections

Post-registration inspections of the pharmacovigilance system are carried out after the issuance of the state registration certificate and are aimed at assessing the fulfillment of the license holder's obligations on pharmacovigilance. Post-registration inspections may be of any type as specified in paragraphs 5.2.1.1 and 5.2.1.2.

#### 5.2.1.5. Announced and sudden inspections

Most inspections of the pharmacovigilance system will be announced, which means that the inspected party will be notified of the need to ensure the participation of relevant persons in the inspection. In some cases, it may be advisable to conduct a surprise inspection or to inform the inspected party prior to the inspection (for example, if the announcement poses a threat to the inspection or the inspection is carried out for a short period of time due to security risks).

#### 5.2.1.6. Repeated inspections

Repeated inspections may be carried out on a regular basis as part of a program of scheduled inspections of the pharmacovigilance system. Risk factors should be assessed to determine the priorities of re-inspections. An early review may be conducted if a significant number of discrepancies have been identified and confirmation of the need to eliminate objections and to ensure compliance with the requirements and obligations of the pharmacovigilance system on a regular basis, including the assessment of changes in the pharmacovigilance system. It is also advisable to re-inspect at an early stage if there is information that the inspected

party has not taken Good corrective and preventive measures in accordance with the instructions of the previous inspection shortly after the previous inspection.

#### 5.2.1.7. Remote inspections

These are inspections of the pharmacovigilance system carried out by inspectors in the absence of the holder of the license or other organization to which the authority to exercise pharmacovigilance functions has been transferred. Communication tools such as the Internet or telephone can be used to perform this inspection. This type of inspection can also be used in exceptional cases in case of logistical difficulties in conducting on-site inspections. The decision to conduct a remote inspection of the inspectors must be agreed with the Authority instructing the inspection. The logistical aspects of the remote inspection must be agreed with the licensee. If there are issues requiring the assessment of the pharmacovigilance system directly at the place of implementation during the remote inspection, a decision shall be made to conduct the inspection by going to the inspection site.

#### 5.2.2. Planning inspections

5.2.2.1. The planning of inspections of pharmaceutical control systems should be based on a systematic approach to risk assessment in order to ensure a high level of protection of public health and the optimal use of resources in the activities carried out to control it. A risk-based approach to inspection planning allows to determine the frequency, direction and scope of inspections of pharmacovigilance.

5.2.2.2. The following factors may be taken into account by the Agency during the development of inspection programs of the pharmacovigilance system:

##### 1) inspection factors:

- history of discrepancies in the results of previous pharmacovigilance inspections or other types of inspections (for compliance with GCP, GMP, GLP and GDP requirements);
- date of re-inspection recommended by inspectors or experts based on the results of the previous inspection;

##### 2) factors related to medicines:

- registration of a medicinal product for which additional pharmacovigilance measures or risk mitigation measures are envisaged;
- conducting post-registration safety surveys or registration of a medicine for which additional monitoring is prescribed;
- registration and delivery of medicines (s) with a large sales volume, ie with a potentially significant impact on a large population of patients;
- Medicinal product (s) that do not have a sufficient number of alternatives in the medicine market of the territory of the Republic of Azerbaijan;

##### 3) Factors related to the license holder:

- Permit holder whose pharmacovigilance system has never been inspected;
- License holder with a large number of medicines in circulation in the territory of the Republic of Azerbaijan;

- holder of a certificate that previously did not have a certificate of state registration in the territory of the Republic of Azerbaijan;
- Negative information obtained from other competent authorities, as well as from other competent authorities regulating the conduct of medicines (ie GCP, GMP, GLP and GDP), on compliance with the requirements of the legislation and / or safety of medicines;
- changes in the organizational structure of the license holder, such as mergers and acquisitions;

4) factors related to the pharmacovigilance system:

- holder of a license with a subcontractor and / or several organizations involved in the implementation of pharmacovigilance activities for the implementation of pharmacovigilance activities (submission of safety reports on the functions of the person responsible for pharmacovigilance in the territory of the Republic of Azerbaijan, etc.);
- replacement of the person responsible for pharmacovigilance from the last inspection;
- changes in the database itself or in interconnected databases, changes in the validity status of the database, as well as in the database (s) on the safety of the medicinal product, which may include changes in the transmitted or transferred data;
- changes in contractual relations with pharmacovigilance service providers or in the places of execution of pharmacovigilance functions;
- transfer of management authority of the main file of the pharmacovigilance system.

5.2.2.3. The entity has the right to request information from licensees that is not available at the time of planning in order to schedule inspections in accordance with the risk assessment approach.

### **5.2.3. Inspected objects**

Any party carrying out, in whole or in part, pharmacovigilance measures on behalf of the licensee, may be subject to inspection to ensure that the licensee is able to comply with the requirements of the legislation on the pharmacovigilance system and reliably fulfill its obligations. Objects to be inspected may be located in the territory of the Republic of Azerbaijan or outside its borders. Inspection of facilities outside the territory of the Azerbaijan Republic may be appropriate if the main center for pharmacovigilance, database and / or pharmacovigilance activities are located outside the territory of the Azerbaijan Republic. The type and quantity of objects to be inspected should be selected appropriately to ensure that the main inspection objectives are met.

### **5.2.4. Inspection volume**

The scope of the inspection depends on the objectives of the inspection, the scope of previous inspections by the Agency, as well as the type of inspection. The following should be considered when preparing the scope of the inspection:

- information provided in the main file of the pharmacovigilance system;
- information on the functioning of the pharmacovigilance system, for example, information on the compliance of the system with the competent authority;
- specific factors of initiation of inspection (5.2.1.2.).

#### 5.2.4.1. Inspections of standard pharmacovigilance

In the process of standard inspections of the pharmacovigilance system, compliance with the normative requirements for pharmacovigilance (regulatory norms) and the requirements of Good pharmacovigilance practices is checked. Where appropriate, the audit should include an assessment of the following elements of the system:

##### 1) Procedures for working with ICSRs against medicines:

- collection, receipt and exchange of notifications received from all types of sources, facilities and organizations within the pharmacovigilance system, including organizations fulfilling pharmacovigilance obligations for the licensee on a contract basis, as well as other sections of the organization not related to the pharmacovigilance system;
- assessment of the persons submitting the notifications, including the mechanism of obtaining and the procedure for registration of the results of the assessment of persons; terminology used; assessment of seriousness, expectation and cause-and-effect relationship;
- Recording of subsequent observations and outcomes, such as medical confirmation of outcomes and patient reports in cases where the medicine has an effect on the fetus during pregnancy;
- Compliance with the requirements of the legislation on the submission of various types of MFPS to the Organization;
- Documentation and archiving of MFPS;

##### 2) Periodically updated security reports (PSUR) (if applicable):

- completeness and reliability of the entered information, substantiation of decisions on the entered information;
- resolution of issues on changing the security profile, submission of relevant analyzes and measures;
- registration in accordance with the requirements of the legislation;
- timeliness of submission;

##### 3) continuous assessment of security profile:

- use of all information sources for signal detection;
- correct application of information analysis methodology;
- compliance of research procedures and follow-up, for example, implementation of recommendations after data analysis;
- Implementation of RMP or other obligations;

- timely identification of complete and accurate information and its submission to the Agency in response to specific requests for information;
  - inclusion of approved changes in safety notices and information on medicines;
- 4) interventional (if necessary) and non-interventional clinical trials / trials:
- submission of notices of suspected unintended serious adverse effects in accordance with the requirements of the legislation;
  - acquisition, registration and evaluation of additional adverse events identified during interventional and non-interventional clinical trials / trials;
  - submission of the results of research / tests and relevant information on the safety of medicines in the form of a report in accordance with the requirements of the legislation;
  - appropriate selection of reference safety information of the medicinal product, maintenance of the current level of information or safety information for the patient in the brochures of the researcher;
  - inclusion of research / test data in the current assessment of the safety profile of the medicinal product;
- 5) pharmacovigilance system procedures:
- roles and responsibilities of the person in charge of pharmacovigilance, such as access to the quality control system of the pharmacovigilance system, the main file of the pharmacovigilance system, performance indicators and system indicators, audit and inspection reports, as well as their ability to take compliance measures;
  - roles and responsibilities of the license holder in connection with the pharmacovigilance system;
  - support of accuracy, completeness and relevance of information in the main file of the pharmacovigilance system;
  - adequacy and quality of staff training, qualification and experience level;
  - the scope and adequacy of the quality system in relation to the pharmacovigilance system, as well as the implementation of quality control and quality assurance processes;
  - suitability of computerized systems used to perform specific functions;
  - Agreements and agreements with all stakeholders, reflecting the obligations and measures for the implementation of pharmacovigilance, as well as their Good implementation.

The audit includes an assessment of the compliance of the risk mitigation measures with the established requirements.

#### 5.2.4.2. Unscheduled inspections

The scope of the unscheduled inspection will depend on its purpose. Assessed aspects of the system may include those listed in paragraph 5.2.4.1, as well as:

- Involvement and awareness of the person responsible for pharmacovigilance on issues related to specific medicines;

- implementation of measures related to the specific starting factor and / or medicine of the inspection, informing and more in-depth study of decision-making processes and procedures.

#### 5.2.4.3. Repeated inspections

5.2.4.3.1. The following aspects should be taken into account when determining the scope of the re-inspection:

- analysis of the state of the corrective and preventive action plan and / or system developed based on the results of previous inspections of the pharmacovigilance;
- analysis of significant changes in the pharmacovigilance system since the last pharmacovigilance inspection (for example, changes in the pharmacovigilance database, merger or acquisition of the company, significant changes in contract activities, replacement of the person in charge of pharmacovigilance);
- analysis of processes and / or issues related to a specific medicinal product, identified as a result of the assessment of information provided by the licensee or not included in the scope of inspection during the previous inspection.

5.2.4.3.2. The scope of the re-inspection is determined based on the results of previous inspections and may be expanded to take into account a number of factors (for example, the time elapsed since the previous inspection date and, if appropriate, the volume of the previous inspection).

#### 5.2.5. Inspection process

5.2.5.1. Pharmacovigilance inspections should be planned, coordinated, conducted, reported, monitored and documented in accordance with inspection procedures. Exchange of experience with other competent authorities and training of the Agency's inspectors will help to improve and harmonize the conduct of inspections.

5.2.5.2. Procedures for pharmacovigilance inspections of the pharmacovigilance system should include the following processes:

- information exchange;
- planning of inspections;
- pre-registration inspections;
- preparation of inspections of pharmacovigilance systems;
- conducting inspections of the pharmacovigilance system;
- submission of reports on inspections of the pharmacovigilance system and subsequent control;
- priority and informing of pharmacovigilance inspections and results obtained;
- keeping records and archiving of documents obtained as a result of inspections of pharmacovigilance systems;
- sudden inspections;
- sanctions and regulatory / mandatory measures in case of serious violations of the legislation;
- Recommendations on training and exchange of experience of inspectors conducting inspections of the pharmacovigilance system.

5.2.5.3. If necessary, new procedures can be developed.

#### 5.2.6. Monitoring the implementation of inspections

If the inspection reveals non-compliance with pharmacovigilance obligations, further control is required until corrective and preventive measures are fully implemented. The control methods listed below should be considered:

- analysis of the license holder's plan of corrective and preventive measures;
- analysis of periodic reports on the progress of work, if necessary;
- re-inspection to assess the reliability of the corrective and preventive action plan;
- a request for information not previously provided; a request for changes (for example, information on a medicinal product); a request for an impact analysis (for example, the results of an analysis of data not previously included in the analysis when performing the signal detection procedure);
- Request for Good information, including changes to information and / or advertising information provided as part of marketing activities;
- request for a meeting with the licensee to discuss the identified deficiencies / non-conformities and their impact on the action plan;
- other medicine-related activities, depending on the impact of deficiencies / inconsistencies and the results of subsequent activities (this may include activities related to the issuance of recall or registration certificates, or permits for clinical trials).

#### 5.2.7. Activities and sanctions of the institution

5.2.7.1. In accordance with the legislation of the Republic of Azerbaijan, in order to protect the health of the population, the Agency is obliged to ensure the fulfillment of pharmacovigilance obligations by licensees. Measures to be taken in case of non-compliance with pharmacovigilance requirements or non-fulfillment of obligations shall be determined separately for each specific case. The measures to be taken will depend on the potential negative impact of non-compliance / non-compliance on the health of the population, but any non-compliance / non-compliance may be taken into account when taking compulsory measures. If necessary, the Agency is obliged to take necessary measures for the application of effective, proportional and prohibitive sanctions against the licensee.

5.2.7.2. In case of non-compliance with the relevant requirements, the possible options for regulation in accordance with the rules established by the management and, if necessary, national legislation include:

- 1) training and assistance: The Agency has the right to communicate with licensees' representatives (for example, at a meeting) to summarize the identified discrepancies, clarify the legal requirements and expectations of the Institution, as well as to review the corrective and preventive measures proposed by the licensee;
- 2) submission of information to other regulatory authorities within the framework of the confidentiality agreement;
- 3) inspection: inspections of license holders who do not fulfill their obligations / requirements may be carried out in order to determine the degree of non-

compliance with the requirements of the legislation / and to confirm compliance with the requirements of the legislation;

4) application for non-compliance / non-compliance, warning letter or notification of violation: these documents are issued by the Agency, indicating the violated legislation or guidance, on the pharmacovigilance obligations or measures to be taken by licensees, as well as subsequent non-compliance / violations. may be issued with a reminder of the time limits set for the elimination of non-conformities / violations for the purpose of prevention;

5) The Agency may consider the publication of a list of license holders who seriously or permanently violate the requirements of the legislation on pharmacovigilance;

6) measures related to the registration card or application for state registration, for example:

- application of urgent restrictions on the safety profile of the medicine;
- suspension or cancellation of state registration;
- suspension of consideration of new applications for a registration card until the implementation of corrective and preventive measures;
- appointment of pre-registration inspections of the pharmacovigilance system.

7) recall of medicines, for example, if the information on the medicine does not include very important safety warnings;

8) measures related to marketing or advertising information;

9) suspension of clinical trials / trials in the event of amendments to the protocols or changes in the safety profile of a particular medicinal product;

10) administrative fines.

#### 5.2.8. Qualification and training of inspectors

The inspectors involved in the inspections of pharmacovigilance systems must be specialists of the Agency or persons appointed in accordance with national regulations. It is recommended that the appointment of inspectors be based on their experience and the minimum requirements set by the Institution. Inspectors should be trained to the extent necessary to ensure their competence in the areas necessary for the preparation and conduct of inspections, as well as reports on them. They should also be trained in pharmacovigilance processes and requirements so that they are able to assess various aspects of the pharmacovigilance system if they do not have relevant experience.

#### 5.2.9. Quality management of pharmacovigilance inspection process

The quality of the inspection process of the pharmacovigilance system is regulated by the Institution, is one of the issues covered by the quality system of the pharmacovigilance system of the Institution and should be audited.

#### 5.3. Roles of cardholders

The pharmacovigilance system of license holders of medicines registered in the territory of the Republic of Azerbaijan must be inspected. Holders of licenses have the following responsibilities for the inspection:

- 1) Since inspections can be sudden, they are always obliged to be ready for inspections.
- 2) Support the main file of the pharmacovigilance system and submit it at the request of the inspectors no later than 7 calendar days after receiving the request.
- 3) Of the objects selected for inspection, which may include organizations performing pharmacovigilance functions on the basis of an agreement with the license holder, are obliged to ensure the consent to the inspection before the inspection.
- 4) To provide inspectors with any information and / or documentation necessary for the preparation for the inspection or during the inspection at the appointed time.
- 5) To ensure that personnel involved in pharmacovigilance activities or related activities will be present during the inspection and will clarify any issues that may arise.
- 6) Ensuring the Good and timely implementation of the corrective and preventive action plan to address the deficiencies / non-conformities identified during the audit by setting priorities for critical and / or significant deficiencies / non-conformities.

#### **5.4. Inspection fees**

The cost of the inspection is borne by the licensee.

### **6. Audit of the pharmacovigilance system**

#### **6.1. Structures and processes**

##### 6.1.1. Audit of the pharmacovigilance system and its objectives

6.1.1.1. The purpose of the audit of the pharmacovigilance system is to confirm the appropriateness and effectiveness of the application and operation of the pharmacovigilance system through the analysis and evaluation of objective facts, including the quality system of the pharmacovigilance system.

6.1.1.2. Audit in itself is a systematic, systematic, independent and documented process of obtaining and objectively assessing the facts that characterize the operation of a pharmacovigilance system in order to determine the degree of implementation of audit criteria that help to improve process control, management and risk management processes. Audit facts consist of records, documented assertions, as well as other information that is relevant to the audit criteria and can be verified. Audit criteria reflect the performance and control standards of the audited party and the activities in which its performance is evaluated. Audit criteria related to the pharmacovigilance system should reflect the requirements applied to the pharmacovigilance system, including the requirements for the quality system of pharmacovigilance procedures, determined by the requirements of the legislation and Good pharmacovigilance practices.

##### 6.1.2. Risk-based approach to pharmacovigilance system audit

A risk-based approach is an approach that uses methods to identify areas of risk. Risk refers to the likelihood that an event will occur that will affect the achievement of the objectives, given the seriousness of the consequences and / or the likelihood that they will not be disclosed by other means. The risk-based approach to audits focuses on the highest risk areas for the organization's pharmacovigilance system, including the quality system of the pharmacovigilance system. In the context of pharmacovigilance, the primary importance is the risk of harm to public health. The risk is assessed in the following stages:

- planning the audit at the strategic level, the result of which is an audit strategy to be approved by senior management (long-term approach);
- planning the audit at the tactical level, the result of which is the audit program, the definition of audit objectives, as well as the scope of the audit;
- audit plan for individual audit assignments, determination of audit engagement priorities based on risk assessment, use of risk-based research and testing methods, report on audit results according to relative risk level, as well as audit recommendations, operational audit planning.

The risk assessment should be documented for strategic, tactical and operational planning of the audit activities of the pharmacovigilance system in the organization.

#### 6.1.2.1. Strategic audit planning

6.1.2.1.1. The implementation of the audit strategy in itself means the planning of high-level audit activities, usually planned for a period of more than a year, usually 2-5 years. The audit strategy contains a list of audits that may be sufficient to perform. An audit strategy is used to identify areas that are considered appropriate for the audit, the subject of the audit, and the methods and assumptions on which the audit program is based (including, for example, risk assessment).

6.1.2.1.2. The audit strategy should cover the internal controls of all components of the pharmacovigilance system, including the organization of risk management and process management:

- all processes and tasks of the pharmacovigilance system;
- quality system of activity in the pharmacovigilance system;
- interaction and, if necessary, a chain of communication with other departments;
- Pharmacovigilance measures implemented by subordinate organizations or whose executive authority has been transferred to other organizations (eg regional information centers; licensee's branches; third parties such as other licensees and contractors).

6.1.2.1.3. The risk factors to be considered when performing risk assessment procedures include, but are not limited to:

- changes in the legislation on pharmacovigilance;
- transformation, mergers and acquisitions of large-scale reconstruction or other forms of pharmacovigilance system;
- changes in key management functions;

- the risk of a shortage of properly trained and experienced pharmacovigilance personnel (eg significant staff changes, deficiencies in training processes, restructuring, increased workload);
- Significant changes in the pharmacovigilance system after the previous audit (for example, the introduction of a new database on pharmacovigilance activities or a significant update of the existing database, changes in processes and activities, taking into account the new or amended requirements of the legislation);
- the first medicine on the market (for licensees);
- Medicines (s) on sale that require specific monitoring to minimize specific risk mitigation measures or safety profile;
- level of criticality of the process, for example:
  - For the institution: the level of criticality of the field / process in relation to the Good functioning of the national pharmacovigilance system and the overall purpose of the health system;
  - for licensees: the level of criticality of the field / process in relation to the Good functioning of the pharmacovigilance system. When deciding whether to conduct an audit of any branch or third party, the licensee must take into account, among other factors included in this list, the nature and criticality of the pharmacovigilance measures currently being taken by a third party or branch on behalf of the licensee.
- results of previous audits (whether this area / process has been audited before, results of previous audits);
- procedural deficiencies / inconsistencies related to specific areas of activity / processes identified;
- other organizational changes that may adversely affect the area of activity / process; for example, changes in ancillary functions (such as information technology support) may adversely affect pharmacovigilance activities.

#### 6.1.2.2. Tactical audit planning

6.1.2.2.1. The audit program itself is a list of audits consisting of one or more audits scheduled for a specific period - usually 1 year. The audit program should be developed in accordance with the long-term audit strategy. The audit program must be approved by senior management, who is generally responsible for the operational and management structure.

6.1.2.2.2. A risk-based audit program is based on a Good risk assessment and should focus on the following aspects:

- quality system of pharmacovigilance system;
- critical processes in the pharmacovigilance system;
- basic control systems referring to pharmacovigilance measures;
- high risk areas after the application of control procedures and risk minimization measures.

6.1.2.2.3. The risk-based audit program should also take into account the results of previous audits, in particular the incomplete coverage of areas of activity, the

direction of high risks, and the direct indication of those responsible for management and / or the pharmacovigilance system.

6.1.2.2.4. The audit program documentation should include a brief description of each audit plan, including the scope and purpose of the audit. The justification of the timing, frequency and volume of individual audits that are part of the audit program should be based on a documented risk assessment. Audits of the pharmaceutical control system based on risk assessment should be conducted regularly in accordance with the requirements of the legislation. Substantiated changes to the audit program must be reliably documented.

6.1.2.3. Operational level audit planning and reporting

6.1.2.3.1. On-site planning and data collection

An entity shall apply written procedures, taking into account the planning and conduct of individual audits. In addition, the timing of all measures necessary to perform the audit should be set out in the relevant procedures related to the audit. The entity shall ensure that the audits are performed in accordance with the written procedures and the section on sound pharmacovigilance practices.

Separate audits of the pharmacovigilance system should be carried out in accordance with the approved risk-based audit (see: 6.1.2.2) program. When planning individual audits, the auditor identifies and assesses the risks associated with the area under consideration, using more appropriate methods of selection research and testing. The method of performing the audit is reliably documented in the audit plan.

6.1.2.3.2. Report

Auditors' decisions are documented in the auditor's report and communicated to management in a timely manner. The audit process should include mechanisms for communicating audit results to the audited entity, obtaining feedback, and submitting the audit finding to management and stakeholders, including those responsible for the pharmacovigilance system, in accordance with the requirements of the legislation and the recommendations on the audit of the pharmacovigilance system. Audit findings should be presented in accordance with the relative level of risk and should be classified in order to demonstrate their criticality in relation to the risks affecting the pharmacovigilance system, processes and process components. The classification system should be defined in the description of the pharmacovigilance quality system and take into account the following threshold values to be used in subsequent reports:

- seriousness of one or more processes or procedures of the pharmacovigilance system that adversely affect the entire pharmacovigilance system and / or the rights, safety and well-being of patients and / or pose a potential threat to public health and / or the requirements of applicable law the principal deficiency / nonconformity that constitutes the violation is considered critical;
- may adversely affect one or more processes or procedures of the pharmacovigilance system and / or potentially affect the rights, safety and well-

being of patients and / or pose a potential threat to public health and / or or significant deficiencies / inconsistencies that constitute non-serious violations of applicable law are considered significant;

- Unexpected failure / non-compliance of one or more processes or any component of the procedures performed by the pharmacovigilance system with the expected adverse effect on the entire pharmacovigilance system or process and / or on the rights, safety and well-being of patients is considered insignificant.

The management of the audited entity and senior management should be informed without delay of issues that need to be addressed urgently.

#### 6.1.2.4. Activities based on audit results and follow-up audits

6.1.2.4.1. The urgency, operational activities, activities within a reasonable time, as well as the issues that need to be decided or reported urgently, are designed to be performed within a timeframe that is considered Good, appropriate and appropriate to the relative risk to the pharmacovigilance system. Priorities for corrective and preventive action should be identified to address identified critical and significant deficiencies / inconsistencies. The exact timing of activities related to identified critical deficiencies / nonconformities may vary depending on the results and the nature of the planned activities.

6.1.2.4.2. The management of the enterprise is responsible for ensuring the organization of mechanisms that allow it to reliably resolve issues related to the audit results of the pharmacovigilance system. The set of measures should include an analysis of the root cause of the identified deficiencies, an analysis of the impact of the audit findings, and the development of a corrective and preventive action plan.

6.1.2.4.3. Top management and management should ensure that all necessary effective measures are taken to address any deficiencies identified in the audit process. The implementation of agreed measures should be systematically monitored. Information obtained during the implementation of corrective and preventive activities should be communicated to senior management in accordance with the planned activities. Confirmation of the completion of a set of corrective and preventive measures must be documented reliably. The audit program should take into account, as necessary, the potential feasibility of performing control audits in order to confirm the completion of the agreed measures.

#### 6.1.3. Documentation and quality system

##### 6.1.3.1. Powers of auditors and quality management of auditor activities

###### 6.1.3.1.1. Independence and objectivity of audit and auditors' activities

The entity must designate a specific person to be responsible for audit activities in the area of pharmacovigilance. Pharmacovigilance system audits must be independent. Management should ensure and document the independence and objectivity of auditors.

Auditors should be free from interference in determining the scope of the audit, conducting the audit of the pharmacovigilance system and providing information

on the results of the audit. The main report should be addressed to senior management, who is fully responsible for the executive and management structures, which allows the auditor (s) to fulfill their responsibilities and provide an independent and objective audit opinion. Auditors may consult with personnel involved in pharmacovigilance processes, experts, as well as with the person in charge of pharmacovigilance, without prejudice and without affecting the objectivity and quality of work performed.

#### 6.1.3.1.2. Continuous improvement of qualifications, professionalism, experience and qualification of auditors

Auditors must have and maintain the qualifications required for the effective implementation of audit procedures under the pharmacovigilance system, as well as the knowledge, skills and abilities required to participate in them. Auditors should have the competence, skills and knowledge in the following areas:

- principles, procedures and methods of audit;
- existing legislation, guidelines and other requirements related to the pharmacovigilance system;
- pharmacovigilance measures, processes and procedures;
- control systems;
- organizational systems.

#### 6.1.3.1.3. Assessing the quality of the auditor's work

An audit of an auditor's performance can be performed through current and periodic evaluations of all auditors, an analysis of the audited entity, and a self-assessment of the auditor's performance (eg, auditing quality, code of conduct, compliance with audit programs and audit procedures).

#### 6.1.3.2. Audits conducted by external providers of audit services

The main responsibility for the operation and effectiveness of the pharmacovigilance system falls on the enterprise. When an entity decides to apply to external audit service providers to comply with the requirements for an audit of a pharmacovigilance system under this section, the following requirements must be met:

- preparation and requirements of the audit strategy, audit program, individual audit issues and audit risk assessment, which must be submitted by the enterprise to external service providers in writing;
- scope of work, audit assignments and procedural requirements must be submitted in writing by the entity to external service providers;
- the entity must obtain documented confirmation of the independence and objectivity of the external providers of audit services.
- The external provider of audit services must also comply with the relevant sections of the current technical code.

#### 6.1.3.3. Maintenance of audit findings

Audit findings and information confirming the completion of audit activities should be maintained in accordance with the requirements of Section 3.

## **6.2. Audit requirements**

### 6.2.1. License holders

#### 6.2.1.1. Audit requirements

Holders of licenses are obliged to conduct regular risk-based audits of the pharmacovigilance system, including audits of the quality system of their pharmaceutical control system, in order to ensure compliance of the existing quality system with the requirements. Dates and results of audits, as well as control audits, must be reliably documented.

##### 6.2.1.1.1. Person responsible for pharmacovigilance in the territory of the Republic of Azerbaijan

The person in charge of pharmacovigilance should receive a report on the results of the audit of the pharmacovigilance system, as well as provide auditors with information related to the assessment of risks, including information on the status of implementation of corrective and preventive measures. The person in charge of pharmacovigilance should receive information on the results of any audit related to the pharmacovigilance system, regardless of the place of conduct.

#### 6.2.1.2. Institution

##### 6.2.1.2.1. Requirements for the audit

The agency should conduct regular independent inspections of the national pharmacovigilance system, regular audits of its own pharmacovigilance system and risk-based audits of the quality system to ensure compliance with the requirements. Dates and results of audits, as well as control audits, must be reliably documented.

##### 6.2.1.2.2. Accepted methodology

Audits should be based on accepted terminology and methodology to ensure that they are planned, implemented and reported in an agreed and coordinated manner.

### 6.2.2. Requirements for the auditor's report

#### 6.2.2.1. Certificate holder's report

6.2.2.1.1. The licensee must include in the MFPS an explanatory note on the results of a critical and significant audit of the pharmacovigilance system. Based on the results of the audit, the licensee should ensure that an appropriate plan is developed and implemented that describes in detail the corrective and preventive measures. Entries in the MFPS may be deleted once the corrective and preventive measures have been taken in full. Objective information is required to remove any audit-related entry from the MFPS.

6.2.2.1.2. Holders of licenses must ensure that a list of all planned and conducted audits is included in the annex to the MFPS, as well as that all scheduled audits are carried out in compliance with the reporting obligations required by law and internal reporting rules. Dates and results of audits, as well as control audits, must be reliably documented.

#### 6.2.2.2. Institutional report

The entity shall require the obligation to submit an audit finding in accordance with the law and internal reporting rules.

### 6.2.3. Confidentiality

The documents and information collected by the internal auditor should be treated with care, taking into account confidentiality.

## 7. Risk management system

### 7.1. Application

The risk management process consists of three interrelated and recurring stages:

1. Characteristics of the safety profile of the medicine, including known and unknown aspects.
2. Planning of pharmacovigilance activities based on the characteristics of risks and the detection of new risks, as well as raising the level of general knowledge about the safety profile of the medicine.
3. Planning and implementation of risk minimization activities, as well as evaluation of the effectiveness of these activities.

### **7.2. Structures and processes**

#### 7.2.1. Principles of risk management

The main goal of the risk management process is to ensure that the medicine is administered at the maximum possible benefit to a particular medicine (or a combination of medicines) in relation to the risks for each patient and for the target population as a whole. This can be achieved by increasing profits or reducing risks. The risk management process is cyclical and involves the identification and analysis of risks and benefits, assessment of risk-benefit ratio and its optimization, selection and planning of risk characterization / minimization methods, application of risk minimization / characterization measures, monitoring the effectiveness of measures taken consists of repetitive steps to collect data with.

#### 7.2.2. Responsibility for risk management within the enterprise (institution and license holder)

The main enterprises directly involved in the planning of risk management of medicines are the Institution and the license holders.

##### 7.2.2.1. License holders

Regarding the process of risk management of the released medicine, the licensee is responsible for:

- Ensuring regular inspections of risks related to the use of medicines (s) in accordance with the requirements of the relevant legislation and submission of the results to the Agency;
- take all necessary measures to minimize the risks associated with the use of the medicine (s), as well as to obtain the maximum possible benefit, including ensuring the reliability of all information provided by licensees in relation to medicines, as well as its active updating and providing new information as it becomes available.

#### 7.2.2.2. Institution

The Institution's responsibilities with respect to the risk management process are as follows:

- regular monitoring of the benefits and risks of medicines, including assessment of notices of side effects provided by licensees, medical and pharmaceutical workers, patients and, if necessary, obtained from other information sources;
- taking appropriate regulatory measures to minimize risks related to medicines and ensuring maximum possible benefits, as well as ensuring the accuracy and completeness of all information provided by licensees on medicines;
- ensuring the implementation of risk minimization activities at the national level;
- effective exchange of information with stakeholders if new information is available. This includes patients, medical and pharmaceutical workers, patient groups, scientific societies, etc. includes submission of information in the appropriate format;
- Ensuring that all license holders of both original and generic medicines take appropriate risk minimization measures when a risk is identified.

#### 7.2.3. Objectives of the risk management plan (hereinafter RMP)

7.2.3.1. RMP contains information that meets the following requirements:

- to determine and characterize the safety profile of the medicinal product (s);
- to show ways to assist in further characterization of the safety profile of the medicinal product (s);
- to document the measures to eliminate or minimize the risks associated with the use of medicines, as well as to assess the effectiveness of the measures taken;
- to document the fulfillment of post-registration obligations on safe use, applied during the registration of the medicinal product.

7.2.3.2. Also to meet the specified requirements RMP:

- describe known and unknown information about the safety profile of the medicinal product (s);
- Demonstrate the degree of confidence that the efficacy of the medicine demonstrated in the target population during clinical trials will be achieved in daily medical practice and documented the need for efficacy research in the post-registration period;
- plan a method for assessing the effectiveness of risk mitigation measures.

7.2.3.3. RMP is a dynamically changing independent document that must be updated throughout the life of the product. Depending on the medication that requires a periodically updated safety report (PSUR), certain (parts) modules can be used for both purposes.

#### 7.2.4. The structure of the RMP

RMP consists of seven informative parts:

Part I. General information about the medicine

Part II. Security specification

SI Module: Epidemiology of Instructions for Use (s) and Target Populations (s)

Module SII: Preclinical Stage Safety Specifications.

Module SIII: Exposure to medicines in clinical trials

SIV Module: Population not studied in clinical trials

SV Module: Post-registration experience

SVI Module: Additional requirements for security specifications

Module SVII: Identified and potential risks

Module SVIII: Overview of security issues

Part III. Pharmacovigilance plan

Part IV. Post-registration effectiveness research plans

Part V. Risk minimization measures (including assessment of the effectiveness of risk minimization measures)

Part VI. Review of RMP

Part VII. Additions to RMP

When RMP is designed for several medicines, a separate section should be provided for each of these medicines.

7.2.5. Detailed description of each part of the RMP

7.2.5.1. Part I of the RMP "General information about the medicine"

This section should provide administrative information about the RMP, as well as general information about the medicine for which the RMP is prescribed.

The section should include:

7.2.5.1.1. Information about the active substance:

- active substance (s);
- pharmacotherapeutic group (s) (ATC code);
- name of the cardholder;
- International date of birth and country of the medicine (if applicable);
- date and country of commencement of medical application (if applicable);
- The amount of medicines included in the RMP.

7.2.5.1.2. Administrative information about RMP:

- data lock point within the current RMP;
- submission date and version number;
- A list of all parts and modules of the RMP, with information on the date and version of the RMP, for which the part / module was last submitted (updated and) in this context.

7.2.5.1.3. Information on each medicine included in the RMP:

- trade name (s) in the Republic of Azerbaijan;
- A brief description of the medicine, including:
  - chemical class;
  - brief description of the mechanism of action;
  - important information on the composition (for example, the origin of the active substance of biological medicines, appropriate adjuvants for vaccines);
- hints:
- approved (if applicable);

- proposed (if applicable);
- dosing regimen:
- approved (if applicable);
- proposed (if applicable);
- dosage forms and dosage:
- approved (if applicable);
- proposed (if applicable);
- Global regulatory status by country (date of registration / rejection, date of placement on the market, current registration status, explanatory notes).
- information on whether the medicine is under special control.

#### 7.2.5.2. RMP Part II "Safety Specifications"

The purpose of this section is to provide a brief overview of the safety profile of a medicinal product (s) with known safety information, as well as to identify insufficiently studied sections of the profile safety. In itself, the safety specification should provide an overview of the important identified risks, significant potential risks and critical missing information of the medicine. The safety specification in the RMP forms the basis of the pharmacovigilance plan and the risk minimization plan.

The security specification in the RMP includes eight sections.

- SI Module: Epidemiology of Instructions for Use (s) and Target Populations (s)
- Module SII: Safety specifications of the pre-clinical stage.
- Module SIII: Exposure to medicines in clinical trials
- SIV Module: Population not studied in clinical trials
- SV Module: Post-registration experience
- SVI Module: Additional requirements for security specifications
- Module SVII: Identified and potential risks
- Module SVIII: Review of security issues

The safety specification may contain additional elements depending on the characteristics of the medicine, its quality aspects and their impact on the safety profile and effectiveness of the medicine, its development and research program, risks associated with the release form and other aspects that change the safety profile.

##### 7.2.5.2.1. RMP SI Module "Epidemiology of Instructions for Use (s) and Target Populations (s)"

The epidemiology of the indication (s) is the subject of description and evaluation in this section. The description should include an assessment of the incidence, prevalence, and mortality of co-morbidities prevalent in the target population, and should be presented as far as possible by age, sex, race, or ethnic origin. Differences in epidemiology in different regions should also be assessed and described. Information on important co-morbidities of the target population and the possible effects of the medicine on the pathology should also be provided.

Information should be provided on whether the medicine is intended to be prescribed, for example, for the prevention of disease, the elimination of some serious consequences associated with specific diseases, or the inhibition of the development of chronic diseases. A brief overview of the medicine's place in the therapeutic arsenal of medicines should also be provided.

#### 7.2.5.2.2. RMP Module SII "Safety specifications of the pre-clinical stage"

This RMP module should provide a summary of important information obtained from pre-clinical safety studies and illustrated below:

- information on the study of toxicity (basic data on toxicity obtained during the study, for example, in the study of chronic toxicity, reproductive toxicity, embryotoxicity, teratogenicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
- information on general pharmacological properties (for example, effects on the cardiovascular system, effects on the nervous system, including prolongation of the QT interval, etc.);
- information on medicine interactions;
- other information on toxicity.

The section should contain information on the relevance of the results and significant toxic properties when used on humans. The importance of the data is determined by the experience of using the appropriate approach or combination of therapies when using the same group of medicines, the characteristics of the medicine and the characteristics of the target population. However, quality aspects should be discussed if the medicine may adversely affect the safety profile (eg, important information about the active substance or its mixtures, such as genotoxic compounds). When the medicine is intended for use in women of reproductive age, the document should contain information about reproductive toxicity and effects on fetal development, as well as the results of use of the medicine in a given group of patients. Other specific groups of the population should be considered in terms of approved guidelines and target populations, as well as the need for pre-clinical data availability.

#### 7.2.5.2.3. Module SIII of RMP "Exposure to medicines in clinical trials"

The section should provide information on patients involved in clinical trials / trials (on which patient group the medicine was studied). The data should be presented in a format suitable for analysis, such as tables / graphs. The size of the study population, data on the number of patients, and the time interval (patient / year, patient / month) when patients were exposed to the medicine should be described in detail. Data on populations included in clinical trials / trials should also be stratified according to the type of study / trial (random blind study and populations included in all clinical trials). Stratification of population subgroups, as a rule, includes:

- age and sex;
- instructions;

- dose;
- hereditary origin.

The duration of the effect should be described either in a graphical format (by including points appropriate to the number of patients and time in the graph) or in tabular format.

If necessary, information on the study of the impact on individual population groups (pregnant women, lactating women, patients with renal insufficiency, liver failure, cardiovascular disorders, subgroups with appropriate genetic polymorphism) should be provided. The severity of renal, hepatic, and cardiovascular dysfunction, as well as genetic polymorphism, should also be indicated.

Categories relevant to the target population should be selected when providing age information. Data on pediatric and elderly patients should be divided according to accepted age categories (for example, 65-74, 75-84, and over 85 for elderly patients). The stratification of medicines with teratogenic effects should be based on the age category of the female part of the population, according to their reproductive potential. Final results should be presented at the end of each table / chart as needed.

Except where justified, clinical trial data should be presented in aggregated form, with a summary of graphs and sections. If the same patient group is included in more than one study (for example, the continuation of open observation after the end of the clinical trial), it is included in the age / sex / race group table once. If there is a discrepancy between the tables according to the number of patients, appropriate explanations should be given.

If the RMP is submitted with an application for a new indication, information on the new dosage form, as well as the method of injection, and clinical trials specific to the instruction, should be provided separately at the beginning of the schedule, as well as in free tables.

#### 7.2.5.2.4. RMP SIV Module “Population not studied in clinical trials”

The SIP module of the RMP should indicate which patient subgroups of the target population have not been studied, or which have been studied only to a limited extent within the patient groups included in clinical trials / trials. Also, the limitations of clinical trials / trials should be presented in terms of inclusion and exclusion criteria for target populations, as well as differences that may arise depending on test parameters (e.g., hospital experience or general practice). Considerations for the possibility of predicting safety for target populations should be based on an accurate and detailed assessment of the limitations of existing data from clinical trials or their absence in relation to any subgroup. Information should also be provided on the limitations of the clinical database in order to identify additional effects for the following reasons:

- number of patients included in the research;
- cumulative effect (for example, specific organotoxicity);

- duration of use (for example, assessment of carcinogenicity).

If missing information can pose a serious risk to the target population, it should also be included in Section SVIII of the risk management plan as a security issue.

The groups of patients under consideration should include (but not be limited to):

***a) Pediatric population***

Children (from birth to 18 years, different age categories or other groups important for development, if necessary, taking into account the specific stages of development)

***b) Elderly patients***

Outcomes of medicine use in patients over 65 years of age should be evaluated; this should be taken into account by older members of the given group.

For a given population subgroup, the assessment of concomitant pathology or organ dysfunction is based on the simultaneous presence of some possible factors, such as multicomponent medicine therapy and multiple concomitant pathologies that simultaneously alter the safety profile of the medicine. In a given subgroup of patients, the need for routine laboratory screening should be assessed when prescribing to patients. Additional effects that may pose a particular risk to elderly patients, such as dizziness or central nervous system effects, should be considered separately during the assessment.

***c) Pregnant or lactating women***

If the target population includes women of reproductive age, the results of the medicine during pregnancy and / or lactation should be considered. If the medicine is not specifically intended for use during pregnancy, the results of all registered pregnancies should be evaluated in the course of clinical trials of the medicine. When reviewing the course of pregnancy, the inclusion in the clinical trial should include an analysis of the reasons for the failure of contraceptive measures (if applicable) in the case of contraceptive use, as well as the results of use in less controlled conditions of daily medical practice.

***d) Patients with hepatic impairment***

***e) Patients with impaired renal function***

***f) Patients with other significant co-morbidities (eg, patients with cardiovascular pathology, immunodeficiency)***

***g) Patients whose disease severity differs from that studied in clinical trials***

Any experience should be considered in patients with varying degrees of severity, especially if the stated indication is limited to patients with a specific severity of the disease.

***h) Patients with known and relevant genetic polymorphism carriers***

The level of pharmacokinetic effects, use in patients with unknown or different genotypes, and the results of the use of genetic biomarkers in the target group of patients should be reviewed. The potential impact on the target population should be assessed, as well as the likelihood of a safety problem with the use of the medicine in patients with unknown or different genotypes.

If a potentially clinically significant genetic polymorphism has been identified during a clinical development program but has not been fully studied, this should be considered as a lack of information and / or potential risk. This information should also be included in the safety specification and pharmacovigilance plan. The identification of this condition as a safety problem is assessed on the basis of the clinical significance of the possible outcomes.

***i) Patients of different heredity and / or ethnicity***

Experience in patients with different hereditary and / or ethnic backgrounds, as well as the effect of this difference on efficacy, safety, and pharmacokinetics in target populations, should be considered. Where hereditary or ethnic differences are likely to affect the efficacy of a medicine, the feasibility of conducting post-registration efficacy studies is assessed.

**7.2.5.2.5. RMP SV Module “Post-Registration Experience”**

The purpose of this RMP module is to collect information on the number of patients to whom the medicine is prescribed at the post-registration stage, the characteristics of use in post-registration medical practice, as well as safety information for specific patient groups specified in the RMP SIV Module. is to provide information on the number of patients included in the observational studies / trials for which regulatory measures have been taken for adaptation;

- SIP Module of RMP, sub-section “Activities and regulatory activities of the licensee related to the safety of medicines”

The subsection lists all regulatory activities (including those initiated by the licensee) in any pharmaceutical market related to the identified safety issues. This list should include a list and description of regulatory activities, indicating country and date. When preparing a RMP update, this section should include a brief description of the activities taken since the last RMP submission and their reasons.

- SIP Module of RMP, subsection “Results of post-registration use obtained outside of clinical trials”

Based on the results of the sale of the medicine in various pharmaceutical markets, the licensee provides general information on the number of patients affected at the post-registration stage. Where possible, this information should be stratified into appropriate categories, including age, sex, indications, dosage, and geographic location. Additional variable information (eg number of vaccination courses, route of administration, or duration of treatment) may be required depending on the medication. Based on application characteristics and target populations, the impact should be quantified and differentiated using a reasonable calculation methodology. It is possible to calculate the amount of medicine sold by weight / quantity and the ratio of the recommended average dose, only if the medicine is prescribed in all cases as a single dose and has the same fixed course of administration / appointment, which is the case for most medicines. can not be applied to the view.

The calculation of the effect on medicines with different uses should be performed separately, if possible. The entity may require additional stratification of impact data, such as impact data for different age groups or within approved guidelines. However, if the medicine is used in different dosing regimens for different indications, or if there are other factors that meet the stratification criteria, the licensee should, if possible, provide information in advance with appropriate stratification (stratification).

- RMP SV Module, “Results of post-registration experience in a group of unstudied patients during clinical trials / trials” subsection

If the post-registration use of the medicinal product is recorded in a specific group of patients identified as having limited or no exposure in the SIP Module of the RMP, the method of calculation and effect, regardless of whether the medicinal product is used according to approved indications or out of instruction Information on the assessment of the number of exposed patients should be provided. When used in the pediatric population, the SVI Module of the RMP should refer to the subsection "Special aspects of application in pediatrics". Also, information on the safety profile of the medicine should be provided for this particular patient group compared to the rest of the target population. The subsection should provide any information on possible changes in the benefit profile (efficacy profile) in a particular group of patients. Also, any specific group of patients at increased or decreased risk depending on a particular aspect of the safety profile should be considered in the RV SVI Module as part of a specific risk assessment, but this section provides guidance on risks and patient groups exposed to them.

- SIP Module of RMP, sub-section “Approved usage instructions and actual use”

In order to update the safety specification, specific references should be provided in medical practice to the extent to which actual use differs from the intended use and approved use instructions (s) and contraindications (s) in RMP Module SVII (use outside approved guidelines). The section includes information on medicine use research (or the results of any other observational research, including the study of medicine use guidelines), as well as medicine use research conducted for purposes other than risk management at the request of the competent authorities.

Non-approved use includes, among others, unapproved use in pediatric patients of different age categories, as well as the use of the medicine in accordance with the instructions not approved in the instructions for use of the medicine, if performed outside clinical trials / trials.

If the institution has concerns about the use of a medicinal product outside of the approved instructions, the licensee should attempt to quantify the use, indicating the method of assessment used to obtain the data.

- SIP Module of RMP, subsection "Use in epidemiological research"

This subsection contains a list of epidemiological studies that have collected / evaluated safety data collection and evaluation. Name and type of study (eg cohort study, case-control type), population studied (including country and other relevant

population characteristics), duration of study, number of patients in each category, number of cases if necessary and information on the status of the study (completed or ongoing). If the study is published, a reference should be made to this section of the RMP, and a relevant publication should be provided in RMP Annex 7 (Part VII. Appendices).

#### 7.2.5.2.6. RMP's SVI Module, "Additional Security Specification Requirements" section

##### - RMP SVI Module, subsection "Potential risk of overdose"

Particular attention should be paid to medicines that have a potential risk of overdose, both targeted and accidental. Examples include medicines with a narrow therapeutic range or medicines that can cause significant dose-dependent toxic reactions and / or are associated with a higher risk of overdose in the target population (e.g., during depression). In the event that the risk of overdose is identified as a safety issue, additional measures are proposed in addition to the relevant risk minimization measures outlined in Part V of the RMP for a given safety aspect.

##### - RMP SVI Module, subsection "Potential risk of transmission of infectious agents"

The licensee must assess the potential risk of transmission of infectious agents. This may be due to the nature of the production process or the materials used. In the case of vaccines, any potential risk of transmission of the live virus should be considered.

##### - RMP SVI Module, subsection "Potential risk of abuse and use for illegal purposes"

The sub-section should assess the potential risk of abuse and illicit use. Where necessary, the RMP should include measures to restrict such actions, such as the use of colorants and / or flavorings in medicinal form, limited packaging size, and controlled distribution.

##### - RMP SVI Module, subsection "Potential risk of errors in prescribing / taking medicines"

Licensees should regularly consider the possibility of errors when taking medications. In particular, before a medicine enters the pharmaceutical market, they must assess the common sources of errors in prescribing / taking the medicine. During the development and design phase of the medicinal product, the applicant must take into account the possible causes of errors in the acceptance of the medicinal product. Consideration should be given to the name of the medicine, the characteristics of the dosage form (eg, size, shape and color of the medicine and packaging), instructions for medical use (eg, solution, parenteral injection, dose calculation) and labeling. Requirements for patient information and label readability should be observed. Consideration should also be given to avoiding such misuse when there is a potential risk of serious harm due to the misuse of the medicine. This concern is particularly justified when the concomitant use of a

medicinal product with other medicinal products prescribed by any dangerous injection is part of routine medical practice. The risk of errors in prescribing a medicine should be considered as a safety concern.

In the presence of different dosage forms of the medicine, the adequacy of the visual (or physical) distinction between medicines with different doses and, as a rule, medicines prescribed or used at the same time is assessed. When there are other medicines in the pharmaceutical market with the same active ingredient whose bioequivalence has not been confirmed, precautions and risk minimization measures should be put in place to prevent medical errors.

When the medicine is planned to be used in a group of visually impaired people, special attention should be paid to the possibility of errors in the administration of the medicine, which should be considered as a safety concern when determining risks.

Risks such as accidental ingestion or other inappropriate use by children and measures to prevent them are assessed.

Errors in medicine administration identified during product development, including clinical trials / trials, should be considered, as well as information about the errors themselves, their potential causes, and ways to remedy them. If necessary, it should be indicated in what form the above was taken into account in the final stages of medicine development.

If additional effects are identified as a result of medical errors in the post-registration period, this topic should be taken into account when updating the RMP and ways to minimize errors should be suggested.

The risk of errors in the administration of the medicine if the composition or dosage of the medicine has changed should be considered as a safety issue; The measures to be taken by the licensee to prevent confusion between the old and new medicines are given within the risk minimization plan. The appropriateness of the risk minimization activity should be assessed within the form of release of the medicinal product, the size of the package, the route of injection or other characteristics of the manufactured medicinal product.

When a medicine is to be used in conjunction with a medication (whether or not it is installed), all risk factors (failure of the medication) that may pose a risk to the patient should be considered.

- RMP SVI Module, "Special aspects of use in pediatrics" subsection

This subsection examines aspects of pediatric use that are not covered in the SIV Module of the Risk Management Plan.

a) Problems identified in the pediatric research plan

The subsection provides any recommendations for long-term follow-up monitoring of safety and efficacy during use in patients from the pediatric population. If this aspect is no longer a safety precaution, an appropriate explanation and justification should be provided.

Proposals for certain long-term pediatric studies / trials should be considered when submitting an application for inclusion in pediatric indications, and appropriate justification should be provided if there is any doubt as to their necessity.

b) Potential for pediatric use outside of approved guidelines

The risk of over-the-counter use of the medicine in the pediatric population or any part of it should be assessed if the nosology, which is an indication for approved use of the medicine, is also found in the pediatric population, but the latter has not been approved for use. All possible directions of application of the medicine in the section "Post-registration experience" of RMP (see: 7.2.5.2.5. SV Module of risk management plan) and "Results of post-registration experience in a group of patients not studied during clinical trials / trials" (see: 7.2 .5.2.5. SV Module of the risk management plan).

- RMP SVI Module subsection "Predictable post-registration use"

In order to make significant changes to the pre-registration RMP or to the instructions for medical use, the licensee must provide detailed information on the intended route of application, the expected use of the medicine by patients over time, and the medicine's position in the therapeutic arsenal.

a) Potential for use outside of unapproved instructions

A potential assessment should be made for the use of the medicine outside the approved instructions.

7.2.5.2.7. RMP Module SVII, "Identified and Potential Risks"

This RMP module provides information on important identified and potential risks associated with medicine use, including identified and potential side effects, identified and potential interactions with other medicines, foods, and other products, as well as the pharmacological class. contains information about the effects.

1) Sub-section "Identified new risks" of RMP Module SVII

The security issues identified after the last submission of the RMP should be listed in this section and evaluated in detail in the relevant section below. The cause of the security problem in the department; Indicate whether the given aspect of the risk is an essentially identified or significant potential risk; substantiation is given for new specific studies / trials on a given aspect of risk or for possible necessary risk minimization measures.

2) Module SVII of the Risk Management Plan Subsection "Detailed Information on Important Identified and Significant Potential Risks"

The section provides detailed information on the more important identified and significant potential risks. This section should be brief and should not in itself contain a selection of information from tables and lists of side effects resulting from clinical trials, or the proposed or actual content of the "Side effects" section of the medicine's instructions for use.

The concept of critical risk also depends on several factors, including the impact on the patient, the severity of the risk, and the impact on the health of the

population. As a rule, any risk that should / should not be included in the instructions for use of medical contraindications or warnings and precautions should be included in this section. Important clinically significant interactions and important pharmacological class effects should also be included in this section. In addition, they are usually mild enough to require special warning or precaution, but occur in a significant portion of the population studied, affect the patient's quality of life, and can have serious consequences in the absence of Good treatment (eg, chemotherapy or other medicine therapy). associated severe nausea and vomiting) risks should be considered for inclusion in this section.

The risks associated with the disposal of used medicines should be considered in relation to some medicines (for example, for transdermal patches). There may also be environmental hazards during the disposal of a medicine, such as a substance that is particularly hazardous to aquatic flora and fauna and should not be disposed of in landfills due to known harmful effects on the environment.

Provision of risk information:

Where appropriate information is available, detailed risk information should include:

a) Speed;

- impact on public health (weight and severity / reversibility / outcome);
- impact on the individual patient (impact on quality of life);
- risk factors (including patient-related factors, doses, risk cycle, additive or synergistic factors);
- preventability (ie, predictability, early detection or development prevention);
- possible development mechanism;
- data source and level of evidence.

Information on the frequency of development should be recorded, taking into account safety information and indicating the source. The development frequency should not be evaluated on the basis of information contained in spontaneous notifications, as this method does not allow the frequency parameter to be evaluated at the required level of reliability. If it is necessary to determine the exact frequency relative to critical identified risks, it should be based on systematic studies (e.g., clinical trials / trials or epidemiological studies) in which the exact number of patients exposed to the medicine and the number of patients identified with the relevant identified risk are known.

The denominator should be expressed using the appropriate units of measurement: for example, the number of patients, the number of patient days, or equivalent units (courses of treatment, prescriptions, etc.). Indicate which frequency indicators are used (indicate the unit of measurement for the denominator). Reliability intervals should also be specified. When using the unit of measurement "number of patients in a given period of time", it is necessary to rely on the assumption that the risk function is practically stable over time. Otherwise, it must be divided into the relevant categories in which the stability assumption is realized. This can be

especially important when the duration of treatment is a risk factor in itself. If necessary, a higher risk period should be identified.

The frequency of the identified risk should be presented in relation to the population as a whole and to the relevant population subgroups.

With respect to essential identified risks, the comparison group should provide information on the increase in the frequency of such risks. Data on the time before the development of side effects should also be summarized using survival assessment methods. The aggregate risk function can be used to provide information on the cumulative probability of the development of side effects.

Information on baseline frequency / prevalence in the target population should be provided for potential risks.

For most RMPs containing individual medicines, the risks associated with direct use or composition are usually considered as separate safety concerns, such as accidental intravenous injection, both oral and subcutaneous injection for a separate medicine in itself. can have a security problem as well as in terms of forms.

It may be appropriate to classify the risks in order to indicate which risk is associated with which medicine in relation to an RMP involving several medicines, which may have significant differences in terms of identified and potential risks. It is recommended to consider the following headings:

- Risks associated with the active substance

This category may include significant identified or potential risks that are common to all medicine formulations, methods of administration, and target groups of the population. Most likely, the scope of this category will include most of the risks that are characteristic of the vast majority of medicines.

- Risks associated with a specific composition or method of injection

Examples include RMPs, which include two medicines, for example, a long-acting intramuscular injection form and an oral form. Additional problems with accidental intravenous administration are unlikely to be related to oral medications.

- Risks associated with the target population

The most obvious example of a target population is the additional physical, mental, and sexual development risks that may occur in the pediatric population. These risks will not be limited to adult medications.

- Risks associated with the transition to over-the-counter medication

3) RMP Module SVII, subsection “Identified and potential interactions involving interactions with other medicinal and food products”

Identified and potential pharmacokinetic and pharmacodynamic interactions should be reviewed both for approved treatment regimens and for the most commonly used medicines in the target population. For each of them, the existing data and evidence base confirming the interaction and possible mechanism should be summarized. Potential health risks occurring under different guidelines and in

different groups of the population are assessed. Clinically significant interactions should be included in the RMP's Identified and Potential Risks section.

#### 4) RMP Module SVII, "Pharmacological Class Effects" subsection

This subsection provides a description and assessment of the significant risks specific to the pharmacological class. During the use of the medicine, the correlation between the frequency of development of side effects and the characteristic frequency for other medicines belonging to the given pharmacological group is evaluated.

If the general risk for other pharmacological medicines is not considered a safety problem with respect to the medicinal product and is therefore not identified and included in the list of potential risks, evidence supporting the subsection should be provided.

#### 7.2.5.2.8. RMP Module SVIII "Security Problems Review"

The section provides summary information on identified security issues.

Security issues can include:

- significant identified risk;
- significant potential risk;
- important missing information.

If the RMP covers several medicines, it is expedient to subdivide the generalized information on safety issues in the section into subgroups (similar to the presentation of information in the SVII module of the RMP); In this case, the following approach to distribution can be used:

- safety issues related to the active substance;
- safety issues related to the specific composition or method of injection;
- security problems related to the target population;
- safety issues related to the transition to over-the-counter release of medicines.

#### 7.2.5.3. Part III of the RMP "Pharmacovigilance Plan"

The purpose of a pharmacovigilance plan is to determine how the licensee intends to identify and / or characterize the risks specified in the safety requirements in the future. A pharmacovigilance plan is a structured plan designed for the following purposes:

- detection of new security problems;
- further characterization of known security problems, including identification of risk factors;
- Investigation of the actual existence of potential security problems;
- identification of methods for obtaining important missing information.

The pharmacovigilance plan should be based on the security issues summarized in the RMP's SVI module ("Additional Security Specification Requirements").

Pharmacovigilance activities are divided into routine pharmacovigilance activities and additional pharmacovigilance activities. It should list the pharmacovigilance activities planned by the licensee for each security issue. Pharmacovigilance plans should be commensurate with the risks of the medicine. When routine

pharmacovigilance measures are generally considered satisfactory to ensure Good post-registration security monitoring and do not require additional measures (eg security research), it is necessary to rely on “routine pharmacovigilance” to address subsequent security issues.

#### 7.2.5.3.1. Part III of the RMP, section "Routine measures on pharmacovigilance"

Routine measures on pharmacovigilance consist of complex measures regularly carried out by the licensee in order to ensure compliance with the requirements of the legislation on pharmacovigilance in the territory of the Republic of Azerbaijan. PSMF contains detailed information on the systems and processes implemented by the licensee to achieve this goal; this information is not repeated in the RMP.

The Authority may issue recommendations to the Licensee regarding changes in existing procedures for the collection, verification, evaluation and presentation of information on adverse effects obtained under the Spontaneous Notification. In this case, in this section, the licensee provides an explanation of the changes made to the routine measure on pharmacovigilance in accordance with the recommendations of the Agency.

##### a) Special follow-up questionnaire on side effects

When the licensee is required to use special questionnaires to obtain structured information on identified significant side effects, or if he plans to use questionnaires for that purpose, copies of those questionnaires shall be provided in Annex 6 of the risk management plan. must be submitted. The use of special questionnaires for further observation of reported suspicious side effects is a routine pharmacovigilance measure.

#### 7.2.5.3.2. Part III of the RMP, section "Additional measures on pharmacovigilance"

Licensees should assess the circumstances in which additional pharmacovigilance measures are required due to the failure to achieve the objective of reliably assessing / investigating risks through routine pharmacovigilance routine activities. The purpose (s) of additional pharmacovigilance measures, as a rule, differ depending on the security problem to which they are addressed. Research under a pharmacovigilance plan should be related to the safety issues specified in the safety specification, whether the research is aimed at identifying and characterizing risks or evaluating the effectiveness of risk minimization measures. The licensee must include all research / testing aimed at investigating / evaluating the security problem, as well as research / testing that may provide useful safety information, although security issues assessed under the RMP may not be among the research priorities. This includes post-registration safety studies, pharmacoepidemiological studies, pharmacokinetic studies, clinical trials / trials, or additional pre-clinical studies. The requirements of relevant management and legislation should be followed in conducting such research / testing.

Research / test protocols under the Pharmacovigilance Plan should be provided in the RMP appendix.

A summary of reports on the results of research / tests performed as part of additional pharmacovigilance measures should be included in the RMP appendix. The impact of the new data on the benefit-risk ratio of the medicine should be evaluated in detail and improved accordingly, taking into account the safety specifications, pharmacovigilance plan and risk minimization plan, and safety data obtained.

- Special cases on post-registration security research

Studies examining the effectiveness of risk minimization measures, along with specific risk factors, should be included in the pharmacovigilance plan, as well as a detailed description of the risk minimization plan.

- Research on the use of medicines

Research on the use of medicines may be carried out, at the request of the Agency, in order to monitor the use of medicines in the country, often in connection with the assessment of mechanisms for compensation of funds spent by the state on the purchase of medicines. This type of research is not intended to directly address the safety aspects of medicines, but it can provide useful information on the effectiveness of risk minimization measures, as well as the demographics of the target population.

- Joint research

If the safety issue involves more than one medicinal product (or if there are more than one license holder for one active ingredient), the Authority should recommend that license holders conduct joint post-registration safety surveys.

Joint studies may also be necessary when the number of patients is limited (rare diseases) or when adverse reactions are rare. The agency should assist interested cardholders in agreeing to develop a joint protocol for post-registration security surveys and to conduct joint surveys. If the interested cardholders have not yet agreed to establish a single protocol within the relevant period specified by the Institution, the Institution may schedule post-registration security surveys and identify the general basic protocol or the main elements of the protocol to be followed by the licensors within the required period. .

- Register

In itself, the register is a type of cohort study without prospective intervention. It is recommended to consider the inclusion of a comparison group in the register; In this regard, the register of diseases is usually preferred over the register, which is limited to certain medicines. The register protocol should take into account the inclusion in the register of information on patients who have been prescribed appropriate medicines or have the same disease.

#### 7.2.5.3.3. RMP Part III, “Action Plan for Additional Pharmacovigilance Requirements for Security Issues”

Where additional pharmacovigilance measures are available, an action plan for each safety issue should be provided in accordance with the following structure:

- security problem;

- purpose of the proposed activity (s);
- proposed activity (s);
- main stages of evaluation and reporting.

One of the proposed measures for each security issue will always be "routine pharmacovigilance". In addition to listing additional activities in the "Proposed activity (s)" item, Annex 5 of the risk management plan should provide protocols (project or other document) for conducting any research.

7.2.5.3.4. Section III of the RMP "General schedule of additional pharmacovigilance measures" section

This section should provide a general schedule of all additional pharmacovigilance measures, including the planned dates of their implementation.

7.2.5.4. RMP Part IV "Post-Registration Effectiveness Research Plans"

Requirements for post-registration efficacy studies apply only to approved guidelines, not to studies of additional, unconfirmed guidelines. Efficiency studies, which are a special obligation and / or condition for obtaining a state registration certificate, should also be included in this part of the RMP.

7.2.5.4.1. Part IV of the RMP, "Review of Existing Efficiency Information" section

In order to provide an explanation of the proposed efficacy studies and to provide rationale for inclusion in the RMP, this section provides summary information on the proven efficacy of the medicine, as well as an indication of which clinical trials / trials and endpoints the clinical assessment is based on. The endpoints of the clinical study on which the effectiveness assessment is based should be evaluated.

The section provides a brief assessment of the need for further post-registration efficacy research on the following aspects:

- relevance of efficacy data to all patients in the target population;
- Factors that may affect the effectiveness of the medicine in daily medical practice;
- variability of the therapeutic effect in the subpopulation.

This section should provide a general schedule of planned surveys / trials, indicating the times and key milestones. The protocols for the given clinical trials / trials are included in Annex 7 to the RMP.

7.2.5.5. RMP Part V "Risk Minimization Measures"

According to the safety specification, the licensee must assess what risk mitigation measures are necessary for each security problem. The risk minimization plan should include detailed information on the risk mitigation measures to be taken to mitigate the risks associated with each identified security problem. The risk mitigation measures proposed for each security issue may include more than one risk mitigation measure.

Risk minimization measures may include routine risk minimization measures and additional risk minimization measures. All risk mitigation measures must have a clearly defined purpose.

#### 7.2.5.5.1. Part V of the RMP, section "Routine risk minimization measures"

Routine risk minimization measures include measures / activities performed for each medication. Routine activities include:

- brief description of the medicine;
- marking;
- instructions for use of the medicine (for patients);
- packaging size / dimensions;
- regulator status of the medicine.

The instructions for use are an important tool for minimizing risks, as they have a controlled and standard information format for medical staff and pharmacists, as well as patients.

##### a) Package size

Limiting the number of units of a prescribed medicine is one of the routine risk minimization measures. When the dose of the prescribed medicine is limited, the patient is obliged to consult a doctor after a certain period of time, which optimizes the process of monitoring his condition and shortens the period of his absence from appropriate observation. It may also be helpful to release the package in small dosing units (in special cases - in a single dosed unit) if overdose is considered one of the main risks.

##### b) Regulator status

Controlling the conditions under which a medicine is available can help reduce the risks associated with its use or misuse. This can be achieved by regulating the conditions under which the medicine can be prescribed or the conditions under which the patient can obtain the medicine.

When issuing a registration card, detailed information on all conditions and restrictions related to the supply and use of the medicinal product, as well as the conditions under which the medicinal product may be available to patients, must be included. This is usually called the "regulatory status" of the medicine. This status includes information on whether the medicine is sold with or without a doctor's prescription. It can also restrict distribution locations (for example, by restricting application to a stationary facility). Additional conditions should apply to prescription medicines only, or rather, they should be classified as prescription medicines only.

Most security issues can be addressed appropriately when implementing routine risk minimization measures. However, for some risks, routine risk minimization measures may not be sufficient and additional risk mitigation measures may be required.

#### 7.2.5.5.2. Part V of the RIP, "Additional risk minimization measures" section

Additional risk mitigation measures are risk mitigation measures that are not related to routine risk mitigation measures. Additional risk mitigation measures should be proposed when routine risk minimization measures are not sufficient to ensure safe and effective use of the medicine. A number of risk minimization

methods are based on information methods that go beyond the user manual and brief description.

With regard to additional risk mitigation measures, a detailed description and justification of the need for their implementation is provided. This section should only include measures for safe and effective use; they must also be scientifically sound, developed and implemented by qualified professionals.

Additional risk mitigation measures are a condition for obtaining a registration card after agreement with the institution. Where appropriate, full information on additional risk mitigation measures (including a draft version of the training materials) should be provided in Annex 6 to the RMP.

#### a) Teaching materials

Teaching materials should not be advertising. The organization coordinates and approves training materials developed under the risk minimization plan.

For medicines containing the same active ingredient, it is recommended to develop teaching materials and materials for patients as close as possible to the form and content.

#### 7.2.5.5.3. The format of the risk minimization plan (s)

This section should address each security issue identified in the security specification.

The following information must be provided for each security issue:

- description of security problem;
- purpose of the proposed activity (s);
- routine risk minimization measures;
- additional risk mitigation measures (if any), objectives and justification of the need for each additional measure;
- method of assessing the effectiveness of risk minimization measures in terms of achieving the set goals;
- the purpose of risk minimization, ie determination of criteria for assessing the success of the measures taken;
- main stages of evaluation and reporting.

The text provided in the operating instructions for routine risk minimization measures should be accompanied by a detailed description of other routine risk minimization measures proposed in relation to security concerns.

#### 7.2.5.5.4. RMP Part V, Section “Evaluating the effectiveness of risk minimization measures”

Risk minimization measures are activities aimed at preventing the development of side effects, reducing the frequency or severity of side effects, as well as minimizing the impact of adverse effects on the patient when side effects occur. When these objectives are met, evaluation of the effectiveness of risk minimization measures should be performed throughout the life cycle of the medicine to ensure that side effects are minimized and thus the benefit-risk ratio of the medicine is optimized.

When a specific risk mitigation strategy is found to be ineffective, alternative measures should be developed and implemented. In specific cases, the assessment may conclude that risk mitigation measures do not manage the risks to the extent necessary to ensure the use of the medicine if the benefits outweigh the risks, which may necessitate the withdrawal of the medicine from the pharmaceutical market or only in patients whose benefits outweigh the risks. expresses the need to limit it to a subgroup.

#### 7.2.5.5.5. Update the risk minimization plan

It should include an assessment of the routine and / or additional risk minimization measures performed during the RMP update. The results of a formal assessment of risk mitigation measures should also be included in this section. As part of this critical assessment, the licensee must identify and assess factors that contribute to the achievement of the risk mitigation objectives or that reduce the effectiveness of the risk mitigation measures. For each security issue, comments should be made on the possible need to change the risk mitigation measures and / or apply additional risk mitigation measures.

#### 7.2.5.6. RMP Part VI “Review of Risk Minimization Plan”

The RMP review for each medicine should be available to the public. The review should include key elements of the RMP, with particular emphasis on risk minimization measures. As for the safety specification of the medicinal product in question, it should contain important information about the identified and potential risks, as well as missing information.

This section of the RMP should contain the following summary information based on the SI, SVIII modules, parts IV and V of Part II of the RMP:

- review of disease epidemiology;
- generalized information on benefit (efficiency) assessment;
- generalized information on security issues;
- Tables:
- generalized information on risk minimization measures for each security problem;
- post-registration development plan (in terms of safety and effectiveness), which includes a detailed description and explanation of all measures required to obtain a registration card.

#### 7.2.5.6.1. Part VI of the RMP, section "Review of the epidemiology of the disease."

The holder of the certificate must summarize the epidemiological information of the disease / condition indicating the purpose of the medicine, as described in detail in the SI module of the RMP. In this case, the information is delivered to the target population in the form of facts and in an appropriate non-specialized language. This section of the review may be omitted if the medicine is used as a diagnostic tool, used under anesthesia, or has other similar indications not related to a specific disease / condition.

#### 7.2.5.6.2. Part VI of the Risk Management Plan, “Generalized Security Information (in non-specialized language)”

This section should briefly describe security issues in a language that is understandable to the general public. The section also contains a description of the severity and frequency of situations caused by security problems. With respect to significant potential risks, the causes of these risks and possible uncertainties in their assessment (for example, the risk is specific to a given class of compounds but not identified in clinical trials when prescribing a given medicine) should be clarified. In the case of essential missing information, it should be indicated how it may affect the target population and in what form it is reflected in the recommendations (for example, the presence of contraindications, precautionary measures).

#### 7.2.5.6.3. Section VI of the RMP, “Summary Data Sheet on Risk Minimization Measures for Security Issues”

This section should list security issues and provide an overview of the proposed risk minimization measures for each security issue. If there are more than one risk minimization plan (Part V of the RMP), a separate schedule should be provided for each of them.

#### 7.2.5.6.4. RMP Part VI, “Planned Post-Registration Development Plan” section

This section should provide a tabular list of planned activities for effectiveness research and further study of security issues. The purpose is to provide an overview of the planned post-registration development of the medicine in relation to pharmacovigilance and efficacy assessment, as well as to review the key stages associated with each study or event. Given table 7.2.5.3.4. and the tables in Sections 7.2.5.4.1. Each line of the table shows the reason for the study, the name and brief description of the study, the time of implementation and the main stages.

#### 7.2.5.6.5. Part VI of the RMP, "Review of changes to the RMP"

The section provides a list of all significant changes to the RMP in tabular form, in chronological order. The information should include, for example, the date on which new security issues are included in or out of the plan, the dates on which new security studies are added or completed, a brief overview of changes in the risk mitigation plan, and the approval dates for changes.

#### 7.2.5.7. RMP Part VII, “Additions to RMP”

The RMP must have the following attachments (if applicable).

Appendix 1 to the RMP is a structured electronic presentation of the RMP.

RMP Appendix 2: Summary of planned, ongoing and completed pharmacovigilance research / testing programs

Appendix 3 to RMP: Research / testing on proposed, ongoing and completed pharmacovigilance plan

Appendix 4 to the RMP: Special forms of follow-up on side effects

RMP Annex 5: Protocol of proposed and conducted research on Part IV of the RMP

RMP Annex 6: Detailed information on proposed additional risk minimization measures (if applicable)

RMP Annex 7: Other ancillary information (including reference material)

RMP Annex 8: Overview of changes in RMP over time.

#### 7.2.6. Interaction between RMP and PSUR

The main post-registration documents of the Pharmacovigilance are RMP and PSUR. While the purpose of the RMP is to manage and plan the balance of risks and rewards before and after registration, the primary purpose of the PSUR is an integrated risk and benefit assessment after registration; thus, these documents complement each other. The overall safety profile of PSUR is considered as part of an integrated assessment of the risk and benefit of the medicine over a specified period of time, so the overall risk and benefit profile of the medicine will be reviewed here (for a wider range of possible side effects). It is expected that only a small portion of the risks will be classified as significant identified or significant potential risks and will be considered as a security issue within the RMP.

If the PSUR and RMP are submitted at the same time, the RMP should reflect the safety profile and efficiency opinion provided in the PSUR. For example, if a new signal is detected in a PSUR and it is identified as an important identified or significant potential risk, the risk should be included in the security problem in the updated version of the RMP provided with the PSUR. In this case, the pharmacovigilance plan and risk minimization plan should be updated accordingly, reflecting the licensee's suggestions for further investigation of the security problem and related risk mitigation measures.

#### 7.2.7. RMP evaluation principles

The main issues to consider when preparing or reviewing a RMP for a medication are:

##### 7.2.7.1. Security specification

- whether all relevant parts are included in the safety specification;
- whether all relevant information was reviewed during the preparation of the security specification, ie whether there are important (unresolved) issues from other sections of the file that were not considered in the security specification;
- if part of the target population has not been studied, whether relevant safety concerns related to potential risks and missing information have been included;
- what are the limitations of the safety database and what level of reliability does it provide in relation to the accuracy of the assessment of the safety profile of the medicine;
- whether the safety specification includes an assessment of specific risks, such as the use of unapproved indications, the risk of malicious use and dependence, the risk of medical error, the risk of transmission of infectious agents;
- whether the security specification realistically reflects security problems (ie important identified risks, significant potential risks and critical missing information);

- Does the safety specification of the generic medicine cover all the safety issues identified in relation to the reference medicine;
- whether the place of the medicine in the therapeutic arsenal corresponds to the intended purpose and modern medical practice.

#### 7.2.7.2. Pharmacovigilance plan

- whether all safety issues identified by the safety specification are included in the pharmacovigilance plan;
- whether routine pharmacovigilance measures are sufficient (as described in the pharmacovigilance system) or whether additional pharmacovigilance measures are needed;
- whether the pharmacovigilance plan clearly defines and describes pharmacovigilance activities, whether this information is sufficient to identify and characterize risks or to provide missing information;
- Does the RMP contain appropriate and adequate recommendations for the monitoring of medical errors related to the use of the medicine;
- whether the proposed additional research / tests are necessary and / or useful;
- whether the researches proposed in the pharmacovigilance plan are adequate and feasible for research of scientific issues based on the submitted drafts of research protocols;
- Are the relevant key times and stages identified in relation to the proposed measures, presentation of results and updating of the pharmacovigilance plan?

#### 7.2.7.3. Post-registration security research plans

- whether the description of the effectiveness of the medicine and the information on the research on which it is based and the end points of the clinical trial correspond to the content of the file;
- Are any of the proposed studies of an advertising nature (ie research that does not pose a valid scientific question and is intended to increase the demand for the medicine);
- the reliability of the performance data and whether a survey is needed for further performance studies as a condition of obtaining a registration card;

#### 7.2.7.4. Risk minimization measures

- whether the information on the medicinal product adequately reflects all the important risks and important missing information found;
- whether it is necessary to include in the information on the medicinal product potential risks that are quite relevant to the safe and effective use of the medicinal product;
- whether the risk proposals are in accordance with the information and recommendations in the short description of medicines;
- Has the license holder considered ways to reduce the risk of medical errors when using the medicine;

- whether this information is included in the relevant information about the medicinal product, measures (including, if necessary, the design of the device) and the design of the packaging;
- whether the proposed risk minimization measures are adequate and sufficient;
- whether additional risk mitigation measures have been proposed and whether they can be adequately justified and assessed as proportionate to the risks;
- whether a detailed description of the proposed methods for measuring and evaluating the effectiveness of risk mitigation measures is included and whether they are appropriate;
- whether the criteria for assessing the effectiveness of risk minimization measures have been determined in advance.

#### 7.2.7.5. When evaluating the update

- whether new information is included in the security specification;
- whether relevant changes have been made to the pharmacovigilance plan (if necessary in view of new information);
- how effective the risk mitigation measures were;
- if necessary, changes in risk minimization measures have been proposed;
- Does the new data indicate that a formal benefit-risk assessment is required (if this has not yet been done in the PSUR).

#### 7.2.8. Quality systems and document management

Although many experts may be involved in the process of writing a RMP, the main responsibility for its quality, accuracy and scientific completeness rests with those responsible for pharmacovigilance. The cardholder is responsible for updating the RMP when new information is available and must apply the quality assurance principles set out in Section 3.

The cardholder must ensure that the RMP submission procedure is documented and monitored, indicating the dates of submission and the significant changes made to each version of the RMP. These records, RMP and any document related to information within the risk management plan may be subject to review by qualified pharmacovigilance inspectors.

### **7.3. Submission requirements**

#### 7.3.1. Circumstances in which the RMP must be submitted

The provision of a RMP or, where appropriate, updates may be necessary at any time during a medicine's life cycle.

7.3.1.1. When applying for state registration of a medicinal product, RMP is submitted in the following cases:

- when a medicine containing a new active substance, which was not previously registered in the territory of the Republic of Azerbaijan, is submitted for state registration;

- when a medicinal product containing a new combination of active substances not previously registered in the territory of the Republic of Azerbaijan is submitted for state registration;
- when applying for state registration of a medicine of biological origin (biotechnological and similar biological (biosimile));
- when applying for registration of generic medicines, if it is necessary to take measures to minimize the additional risk for the original medicine.

When the benefits outweigh the risks, the Authority may require the submission of a RMP when applying for state registration of a medicinal product in other cases where the provision of medicinal products requires additional pharmacovigilance measures or risk minimization measures.

7.3.1.2. In addition, RMP is provided in the following cases:

a) when making significant changes to the state registration certificate, scope, aspects of the production process:

- new rules of use;
- addition of pediatric indications;
- making significant changes to the instructions for use;
- a new production method for biotechnological or similar biological medicines;
- new dosage form;
- new injection method.

b) at the request of the Institution before or after the state registration if there is a security problem affecting the benefit-risk ratio;

c) if a safety problem is detected at any stage of the medicine's life cycle.

7.3.1.3. Special requirements

As a rule, all parts of the RMP must be submitted. However, some parts or modules may be omitted in accordance with the concept of proportionality in certain cases described below, unless otherwise required by the Institution. However, any safety concerns identified in relation to the reference medicine in the section excluded from the RMP general presentation should be included in module SVIII of the risk management plan, except where they have lost their relevance.

- First time application for state registration of generic medicines

Sections SI-SV of the safety specification may be omitted in the case of the first submission of generic medicines for which RMP is applied to the original medicine. The SVI section of the RMP should be based on the provision of information on the safety problem identified for the original medicinal product, unless the characteristics of the generic medicinal product differ significantly to affect the safety profile or unless otherwise required by the Institution.

Unless additional pharmacovigilance or efficacy studies have been applied to the original medicinal product, Sections III and IV of the RMP and the section on the planned post-registration development plan of Part VI of the RMP may not be provided as conditions for obtaining a registration card.

The RV module SV must be included when submitting RMP updates.

The requirements for the submission of information on the sections of the RMP when submitting an application for state registration are shown in Table 1.

**Table 1 - Requirements for submission of information on sections of the risk management plan when submitting an application for a state registration certificate**

Type of application	I part	Part II. SI section	Part II. Section SII	Part II. SIII	Part II. SIV	Part II. SV section	Part II. SVI part	II part. SVII section	II part. SVIII	III part	IV part	V part	VI part
New active ingredient	+	+	+	+	+	+	+	+	+	+	+	+	+
Generic medicine	+							‡	+	+	*	∫	+
Hybrid medicine	+	†		†				†	+	+	+	∫	+
Fixed combination medicine - with a new active ingredient	+	‡	‡	‡	‡	‡	‡	+	+	+	+	+	+
Fixed combination medicine - does not contain a new active ingredient	+		†	†				‡	+	+	*	∫	+
Medical use is a well-studied medicine	+								+	+	+	+	+
Biosimilar	+		+	+	+	+	+	+	+	+	+	+	+

Note: 1. The "+" symbol indicates that the information in this section is provided in full.

2. The symbol "‡" indicates that the information in this section is provided in the absence of an approved RMP for the reference medicine.

3. The symbol "\*" indicates that the information in this section is provided if post-registration studies to assess efficacy have been prescribed for the reference medicine.

4. The symbol "∫" means that this section may contain a note on the compliance of safety information with the instructions for use and brief description of the medicine.

5. The symbol "†" indicates that the information requirements in this section are based on the principle of proportionality to the risks associated with the new safety data obtained, as well as possible differences with the reference medicine.

6. The symbol "≡" indicates that the information in this section should be presented with an emphasis on the new active item.

#### 7.3.2. RMP update

Each subsequent version submitted shall be in the form of an update, unless the RMP has previously been submitted by the licensee during the registration procedure for the active substance, unless otherwise specified. Each submitted version of the RMP must have an exact version number and date. This applies to the provision of all or only part or all of the RMP. Modified versions with identification information must be accompanied by a cover letter containing a detailed description of the changes since the last version was submitted.

The timing of the submission of RMP updates is determined during its implementation, as well as a condition for maintaining regulatory status. These deadlines are the maximum allowable, and in case of significant changes in the assessment of the risk-benefit ratios of the relevant medicines included in the RMP, the licensee is required to submit the updated RMP outside the scheduled submission schedule and monitor the medicine safety profile. does not absolve from responsibility.

If no changes have been made to the RMP since the last submission (ie the scheduled renewal occurs immediately after the procedure is completed), the holder may submit a letter explaining that there are no changes and may not renew the RMP with the consent of the Institution.

Unless otherwise specified, scheduled updates of RMP should be provided at the same time as PSUR, when PSUR and RMP are essential for the medicine.

Once the RMP is updated, the risk minimization plan should include an assessment of the effectiveness and results of routine and / or additional risk mitigation measures (see: 7.2.5.5.4.).

## **8. Management and reporting of side effects of medicines**

### 8.1. Structures and processes

This section sets out the basic principles for the procedures for collecting, registering and submitting notifications of suspected adverse medicine reactions.

#### 8.1.1. Collection of notifications of side effects

The institution or licensee shall take appropriate measures to collect and manage all notices of suspected side effects associated with the intake of medicines obtained from various sources without request and on demand.

A pharmacovigilance system should be developed to ensure that sufficient reports of side effects are collected and that they are subsequently scientifically substantiated.

The system should be designed to ensure that the quality of notices of side effects collected is reliably assessed against the accuracy, comprehensibility, accuracy, consistency, feasibility of verification and maximum completeness for clinical evaluation.

The system should be set up in such a way as to allow timely validation of reports of suspected adverse effects and their exchange with the Authority and licensees at the time prescribed by law.

#### 8.1.1.1. Unauthorized notifications

##### 8.1.1.1.1. Spontaneous notifications

Spontaneous notification - one or more in a patient sent by a medical worker, patient or consumer to the address of the Institution, license holder or other organization (for example, Regional Center, Toxicology Center) without the request of the latter and prescribed one or more medicines a statement describing the suspected side effects. Notifications received from organized data collection programs or other research are not considered spontaneous.

The primary source of suspected side effects (s) is the person who provided the information about the side effects. If information on the same side effects is received from more than one primary source, such as a healthcare professional, patient or consumer, information on all primary sources should be included in the "Primary Source" section of the side effects notification forms.

Stimulated receipt of "notification letters", publications, inquiries from health care providers, or lawsuits against groups of medications should also be considered as spontaneous notifications.

Notices of side effects from the patient or consumer should be treated as spontaneous notifications, regardless of subsequent medical confirmation.

In the absence of an indication of a cause-and-effect relationship, such an adverse event is considered an additional effect if a spontaneous notification of the development of the adverse event is received. Exceptions are notifications by the sender stating that there is no interaction between the adverse event and the reception of the suspicious medicine.

##### 8.1.1.1.2. Notices of side effects published in the medical literature

The scientific and medical literature is an important source of information for monitoring the safety profile and benefit-risk ratio of medicines, especially in relation to the detection of new safety signals or topical safety issues. Licensees should be aware of possible publications by systematically reviewing widely used databases (eg, Medline, Excerpta Medica, or Embase) at least once a week. When reviewing the literature, the license holder should ensure the use of databases that contain the most article references on the characteristics of the state-registered medicines. In addition, licensees must monitor scientific and medical publications published in local journals in the countries where the medicines are registered and submit them to the company's pharmacovigilance department.

In order to identify and record notices of adverse medicine-related side effects identified during spontaneous or post-registration non-interventional trial, notification of suspected side effects published in the scientific and medical literature, including important summaries or monographs published in conference proceedings should review their projects.

When several publications are mentioned in the publication, the relevant license holder (s) should only review the medicines identified by the author of the publication that have at least a possible cause-and-effect relationship with the suspected side effects found. This also applies to notices published in the scientific and medical literature in the country where the holder has a certificate of state registration of the medicine, but has never sold it.

Notices that are considered valid must be submitted to the Institution in accordance with the requirements of applicable law. The beginning of the notification period for the submission of a notification of an additional effect shall be determined from the moment of obtaining the information on the additional effect, which meets the minimum information requirements for which the holder of the certificate must be notified immediately. An additional adverse event should be documented for each identified patient and the report should provide medical information that is important for evaluation. Reference should be made to the relevant publication as a source of notification of additional effects.

#### 8.1.1.1.3. Notifications from other sources

When a cardholder is notified of a suspected side effect from non-medical sources (eg, non-profile press or other media), he or she should act as a spontaneous notification. Every effort should be made to investigate the incident in order to obtain the necessary minimum information that provides a Good statement of side effects. For other spontaneous reports, the notice periods established by law shall also apply to these reports.

#### 8.1.1.1.4. Information about suspected side effects from the Internet or digital media

Licensees should regularly review Internet resources or digital media under their control or for which they are responsible for potential warnings of suspected side effects. If the digital environment is owned by the licensee, paid for by the licensee and (or) controlled by the licensee, the internet resource is considered to be a resource owned by him. Such regular review of the sources should be ensured in order to meet the requirement that Good notices of potential adverse effects be provided to the Authority from the date of posting the information.

Certificate holders are encouraged to actively monitor specific websites or digital media, such as support groups for certain illnesses or patients, to see if they describe important security issues that may require notifications in accordance with applicable requirements. The periodicity of monitoring of these sites or digital media should be determined based on the risks associated with the monitored medicine.

Notifications of suspicious side effects obtained from Internet networks or digital media without request should also be considered as spontaneous notifications. The notification period established by law for spontaneous notifications shall also apply to this information. The notification author's ability to identify suspicious side effects from the Internet or digital media, ie the ability to verify the accuracy of the report's contact information, depends on the presence of a real person (for example, a valid email address provided). Contact information should only be used for pharmacovigilance purposes. In the absence of a primary source country, the country from which the information was obtained should be used as the primary source country, depending on the location of the monitoring. When a cardholder receives information about a suspected adverse effect described in digital media that is not under the auspices of the company, he or she must evaluate the notice to determine compliance with the emergency notification requirements.

#### 8.1.1.2. Notice of additional effects obtained on demand

Notice of suspected side effects obtained on demand - clinical trials / trials, non-intervention studies / trials, registers, individualized use programs of unregistered medicines, other programs for the use of unregistered medicines in terms of disease monitoring and compassionate emergencies, patients and or notifications received from organized data collection systems, including a survey of health workers or the collection of information on patient dependence or efficacy. Notices of side effects from any of these data collection systems should not be considered spontaneous.

Notice of side effects obtained on request should be classified as notifications obtained during research / testing under the notification procedure and an appropriate cause-and-effect assessment should be performed to ensure that they meet the conditions for immediate notification.

#### 8.1.2. Validation (evaluation) of notifications

8.1.2.1. Only ICSRs with positive validation results should be reported immediately. In order to comply with this requirement, all notices of adverse medicine reactions must be validated prior to their submission to the Authority for the availability of the minimum information required to be reported, and only valid ICSRs must be provided. The minimum information required must be as follows:

- a person who sends a notice (primary source) that can be identified by its name or initials, address or qualifications (eg doctor, pharmacist, pharmacist, other health care professional, patient or consumer or other person who is not a healthcare professional). The person who sent the notification shall be deemed to be identifiable if there is contact information that ensures that the notification can be confirmed or that further observation is carried out if necessary. All parties providing information on the additional impact event, including additional information on the request, must be identifiable. If the person sending the notice does not wish to provide contact information, the notice of additional impact shall be considered valid provided that the organization informed of the incident has the opportunity to confirm it directly with the person notifying;

- a patient who can be identified by indicating his initials, patient identification number, date of birth, age or age group, sex;
- at least one suspicious medicine;
- At least one suspicious side effect.

If the original source makes it clear that there is no cause-and-effect relationship between the medication and the side effects, and the recipient (Authority or Licensee) agrees, the notification is considered invalid because the minimum information required is incomplete. The Notice of Additional Impact (ICSR) is also deemed invalid even if the notification states that the patient has been exposed to an additional effect, but this side effect has not been achieved or a description has not been provided.

8.1.2.2. The term “identifiable” refers to the ability to verify the presence of the reporting person (compiler of the notice) or the patient when collecting notifications of suspected side effects from the Internet or digital media.

8.1.2.3. The absence of any of the four elements of the minimum information required to be reported indicates that the event is incomplete and that the procedure for immediate notification of an additional impact has not been applied. Institutions and licensees should pay due attention to the collection of missing elements in the notifications. However, notices of side effects that incomplete the minimum information required to be reported must be registered within the pharmacovigilance system for use in current safety assessment activities.

8.1.2.4. Even if it is known that a person who notifies one of the parties (the Authority or the licensee) of a suspected additional effect may give notice to the other interested party, that notice shall be treated as a Good notice of the additional effect. The additional impact notice must contain all the information necessary to detect a duplicate of the notice.

8.1.2.5. In the case of unregistered post-registration studies, the event should not be categorized as less Good if there is disagreement between the researcher and the licensee / research sponsor about assessing the cause-and-effect relationship between prescribing the suspected medicine and side effects. The additional impact notice should include the opinion of both the researcher and the registration card holder / research sponsor.

8.1.3. Further work with notifications of side effects

8.1.3.1. When notifications of side effects are received initially, the information they contain may be incomplete. In such cases, further work should be done with such notices in order to obtain additional detailed information that is important for a scientific assessment of the causes of side effects.

8.1.3.2. Subsequent work should focus on optimizing the collection of missing data. Whenever possible, written confirmation of the information provided orally should be obtained. This standard pharmacovigilance activity should be carried out in a way that encourages the primary source (disclosing person) to provide new

information that is important for the scientific evaluation of a particular safety issue.

8.1.3.3. If information that is likely to have an adverse effect is obtained directly from the patient or consumer, if this information is incomplete, an agreement should be reached to contact the appropriate healthcare professional for further information. When such an event, in which the initial notification is made by the consumer or the patient, is confirmed (in whole or in part) by the health worker, the information provided must be accurately reflected in the ICSR.

8.1.3.4. Accurate identification of the relevant medicinal product with respect to the manufacturer of the medicinal product is important in relation to suspected side effects associated with biological medicinal products. For this reason, all necessary measures should be taken to accurately indicate the trade name and batch number of the medicine.

#### 8.1.4. Data management

8.1.4.1. Paper-based notices and electronic information about suspected side effects, including personal data that ensure the identification of patients and whistleblowers, must be kept in accordance with national confidentiality requirements and treated in the same manner as other medical records. Personal information about the medical staff (whistleblowers) who prepare the reports must be kept confidential.

8.1.4.2. Strict control should be exercised over the accessibility of documents and databases to authorized personnel only to ensure the confidentiality and protection of pharmacovigilance information. The requirement for data security applies to all stages of data transmission and handling. In this regard, procedures should be followed to ensure the security and protection of data during transmission.

8.1.4.3. If the transmission of pharmacovigilance data is at the intra-enterprise or inter-enterprise level, a mechanism should be in place to confirm the receipt of all notifications; in which case an approval and / or verification process must be provided.

Additional impact notification information may only be transmitted anonymously to interested parties.

8.1.4.4. Storing information in electronic format should provide "online" access.

8.1.4.5. The terminology usage procedure should be monitored and validated by performing a quality assurance audit in the form of a systematic or periodic selection assessment. The staff should be instructed to enter information on the use of terminology, and staff qualifications should be periodically confirmed. Notices of additional impacts obtained from the primary source (disclosure holder) should be impartial, without the transformation and interference of information processing, as well as the addition of self-additions to such data during data entry or transmission. Notices must contain the original text used by the original source, literally or its exact translation. The original text must be literally coded using appropriate terminology.

8.1.4.6. Electronic storage of information should ensure that all entered or modified information, including the date and source of the data, as well as the dates and places of transmission of the information obtained ("author's footprint") is tracked.

8.1.4.7. Databases should be checked regularly to detect and process duplicate notifications of side effects.

#### 8.1.5. Quality management

8.1.5.1. In order to ensure compliance with the required quality standards at each stage of the conduct of the Institution or Licensees, notifications of additional impacts such as data collection, transmission, management, coding and archiving, event validation, evaluation, subsequent information retrieval and submission of FHTs must have a management system. The relevance of the stored data to the initial notices and notices containing information on subsequent assessments should be verified by means of quality control procedures that allow validation by comparing them with the initial data or their descriptions. In this regard, easy access to primary source information (eg letters containing detailed information about additional effects, e-mail notifications, recording of telephone conversations) or a description of the source information should be provided.

8.1.5.2. Written standard operating procedures should ensure a clear division of roles and responsibilities, and clarity of assignments for all parties. Provisions for Good control and system modifications should be developed and implemented as required. The requirements apply to the activities of third parties under the contract, the procedures of which must be verified to ensure compliance and compliance with the applicable requirements.

8.1.5.3. Appropriate training should be provided to personnel directly involved in pharmacovigilance activities, as well as to other departments that may receive or process safety notices (eg clinical development, sales, medical information, law, quality control). The training should include the relevant requirements of the legislation in the field of pharmacovigilance, as well as special training on the implementation of reporting activities.

#### 8.1.6. Special cases

##### 8.1.6.1. Use of the medicine during pregnancy or lactation

###### 8.1.6.1.1. Pregnancy

In order to gather information on the outcome of the pregnancy and the possible impact on the child's development, follow-up should be provided in cases where the embryo or fetus may be exposed to the medicine (either to the mother or to the father as a result of the medicine).

When the medicine is taken before pregnancy, it should be taken into account when assessing the likelihood of exposure of the embryo to the medicine if the half-life of the active substance or one of its metabolites is prolonged.

Notices of the effects of medications during pregnancy should be provided with more detailed information so that a cause-and-effect relationship can be assessed. Standard questionnaires can be developed and used for these cases.

Certain cases of adverse medicine reactions during pregnancy are classified as serious side effects, which must be reported immediately in accordance with the requirements of the legislation.

This mainly applies to the following cases:

- Notices of congenital anomalies or developmental delays in the fetus or child;
- notification of fetal death or miscarriage;
- Notification of suspected side effects in newborns classified as "serious".

Urgent notification does not apply to other cases, such as notification of termination of pregnancy without information on congenital malformations, notification of pregnancy without information about the outcome, or notification of normal outcome due to the absence of suspicious side effects. However, such notices should be treated as other notices of adverse medicine reactions.

In certain cases, all notifications about the effects of medications during pregnancy may need to be given immediately. This requirement / condition may be included in the RMP and is usually due to the presence of contraindications for use during pregnancy or the apparent teratogenic effect of the medicine and the need for subsequent mandatory careful monitoring (eg, thalidomide, isotretinoin).

The authority should be informed promptly of a possible teratogenic effect (eg, a group of similar anomalous outcomes) to determine the signal.

#### 8.1.6.1.2. Lactation

Suspected side effects in infants as a result of medicine penetration into breast milk should be reported.

#### 8.1.6.2. Use of the medicine in pediatrics and the elderly

When a health worker, patient or consumer reports an incident, every effort should be made to obtain and display information about the patient's age or age group in order to be able to identify potential safety signals that are specific to a particular population.

When used among a group of patients not included in the approved medicine use instructions, it is important that both the Institution and the licensees monitor any subsequent safety concerns and take appropriate action. Licensees and the Authority should encourage the compilation and submission of notifications of all suspected side effects, even if they are in a population not included in the instructions for use of the medicine.

#### 8.1.6.3. Notices of overdose, abuse, malicious use, medical error or exposure to occupational medicines.

Unless an overdose, abuse, misuse, medical error, or exposure to an occupational medicine causes additional effects, they shall not be subject to an emergency notification procedure. When this information can be applied, it should be taken into account in the RMP and in the relevant PSUR.

If the notices contain safety information that affects the benefit-risk ratio of the medicinal product, they should be notified to the Authority in accordance with the requirements of the legislation.

#### 8.1.6.4. Lack of therapeutic efficacy

Notice of the lack of therapeutic efficacy should be recorded and further work should be done to ensure data integrity. These notices, as a rule, are not reported immediately and are taken into account in the PSUR. In certain cases, notifications of lack of therapeutic efficacy may be required within 15 calendar days. These include the use of a suspected medicine in the treatment of life-threatening diseases (including life-threatening infectious diseases caused by susceptible microorganisms or the development of new resistant bacterial strains previously considered susceptible), as well as suspected medicine use. It also includes the lack of therapeutic efficacy in the presence of vaccines or contraceptives.

Ineffectiveness of vaccines should be reported, in particular, to identify potential signals of immunogenicity, immunosuppression, or strain replacement in the vaccine subgroup. Such signals may require further study and operational activities in post-registration security surveys.

#### 8.1.7. Prompt provision of ICSR and other medicine safety information.

Only notifications of validated side effects should be submitted to the institution. The counting of the time of the notification procedure shall begin from the moment of obtaining the minimum information required by the licensee, including medical representatives and contractors, for the submission of notifications. This date is considered the start date of the time count ("day zero").

Where a licensee has established contractual arrangements with a person or organization, there must be clear procedures and detailed arrangements between the licensee and the person or company to ensure that the licensee fulfills its obligations to provide notice of additional effects. These procedures should specify, in particular, security information exchange processes, including timelines and the obligation to notify the Authority of additional effects. Duplicate submission of notices to the Agency shall not be allowed.

The time count ("day zero") for ICSRs described in the scientific and medical literature begins with the date of notification of the publication containing the minimum information required to be reported. Detailed arrangements must be in place to ensure that the licensee complies with the requirements of the reporting law when a contract is entered into with a person or organization to search the literature and / or compile notice of side effects.

When important additional information about a previously reported adverse effect is obtained, the counting of time for the preparation of the subsequent notification shall resume from the date of receipt of the relevant subsequent information. Subsequent information important for the purposes of the notification is medical or administrative information that may affect the assessment or management of the incident or change its severity criteria. Insignificant information may include

updated interpretations of event assessments or corrections to typographical errors in previous versions of the event.

#### 8.1.7.1. Requirements for prompt notification of side effects.

Holders of licenses shall submit to the competent authority within 15 calendar days from the date of receipt of the minimum information (8.1.7.) Required to be notified by the owner of the registration card or his authorized representative:

- notice of serious additional side effects against the medicinal product registered in the territory of the Republic of Azerbaijan;
- notification of unexpected serious adverse effects on the medicinal product registered in the territory of other countries.

The designated time of notification shall apply to the initial and subsequent information on the adverse effects of the medicinal product.

In case of transfer of an additional impact from the category of serious side effects to the category of non-serious side effects, this information must be submitted to the competent authority within a period not exceeding 15 calendar days.

#### 8.1.7.2. Method and form of notification of side effects

Licensee ICSRs must be submitted to the Authority electronically or on paper. The format of FHTs should be in accordance with the E2B format provided for in the International Harmonization Conference (ICH) guideline "Clinical Safety Data Management - Data Elements for the Presentation of FHTs".

#### 8.1.7.3. Requirements for urgent provision of other information on safety of medicines

The following important safety information, which leads to changes in the benefit-risk ratio of the medicine, must be provided immediately within a period not exceeding 15 calendar days:

- increase in the expected frequency of serious side effects that may affect the benefit-risk ratio of the medicine;
- Restriction, revocation, non-extension, cancellation or suspension of the validity of the state registration certificate, initiated by the institution or the licensee of the issued medicine, for reasons related to the safety and effectiveness of the medicine in other countries;
- introduction of significant changes in the recommendations for medical use in the territories of other countries for reasons related to the safety of the medicine;
- a safety problem recorded in the course of post-registration non-intervention trial, clinical trial or pre-clinical research;
- safety information assigned as a result of signal detection activities that may affect the benefit-risk ratio;
- safety problems related to the use of the medicine that does not comply with the instructions for use;
- safety problems related to the instructions for use of the medicine or incorrect information on the labeling;

- Lack of effectiveness (or lack thereof) of medicines used in life-threatening pathologies, including vaccines and contraceptives;
- security problems caused by the supply of raw materials.

Security information shall be provided to the Institution in writing. The above information on the safety or efficacy of the medicinal product shall be provided without delay and as soon as the licensee or his authorized representative becomes aware of it. The information provided should include the above information on safety or efficacy and the proposed measures for the suspected medicine. The specified aspects of the safety profile should be analyzed and reflected in the relevant sections of the medicine PSUR.

## **8.2. Collection of notifications of side effects**

### **8.2.1. Obligations of the institution**

They should have a system for collecting and recording notifications of all suspected side effects detected on the premises and observed by health care providers, patients or consumers or licensees.

The agency should take all appropriate measures to encourage medical personnel in its territory to report notices of suspected side effects. In addition, the Agency may impose special obligations on health workers.

In order to optimize the procedure for submitting information on side effects, web-based standard forms should be accessible through national web portals for medicines, along with information on various methods of providing information on suspected side effects associated with the use of the medicine.

The Institution shall ensure that notices of all serious adverse effects registered in the territory of the Republic of Azerbaijan and submitted to the Institution and validated as valid are included in the database of adverse effects.

Measures should be taken to express appreciation for the work of providing notification of additional effects, including the provision of additional information. In case of notification of additional effects by the license holders, the Authority may involve the licensee in further work on the notifications.

The Authority responsible for the control of the circulation of medicines shall take measures to obtain information on any suspected side effects observed by a specialist of any other body, institution, institution or organization responsible for the safety of patients, and to submit these notices to the national database. Based on the above, in case of sending notices of suspicious side effects directly to other bodies, institutions, organizations and / or enterprises, the competent authority must have an agreement on the exchange of information in order to forward these notifications. This requirement also applies to cases of side effects related to medical errors.

### **8.2.2. Obligations of cardholders**

Each cardholder must have a system for collecting and recording notifications of all suspected side effects, both those submitted by health care providers, patients or

consumers as part of a spontaneous notification, and those obtained during post-registration studies. Licensees should establish mechanisms to monitor notification of side effects and to deal with them in the future.

Obligations of license holders to collect information on suspicious side effects include notifications concerning the name, composition, batch number, admission procedure, country of origin or country of origin of the suspected substance, which cannot be ruled out.

#### 8.2.2.1. Spontaneous notifications

Holders of licenses must register spontaneous notifications of all suspicious side effects occurring in the territory of the Republic of Azerbaijan or outside its borders. This includes notifications of suspicious side effects obtained electronically or by any other appropriate means. Licensees may use their websites to assist in the collection of information on suspected side effects by providing forms for notification of side effects or relevant contact information for direct contact.

#### 8.2.2.2. Notice of additional effects obtained on demand

Holders of licenses must register notices of all suspicious side effects that occur in the territory of the Republic of Azerbaijan or outside it, discovered in the course of post-registration research. Notices received as a result of organized data collection initiated, managed or funded by cardholders are among the notifications received on request. They also include post-registration non-interventional trial, humanitarian emergency use programs, individualized unregistered medicine use programs, patient support and other disease monitoring programs, registers, patient support programs, and collection of information on patient adherence or effectiveness. is.

As in the case of a spontaneous notification, cardholders must have a complete and comprehensive mechanism for collecting information on the notification received at the time of the initial notification in order to ensure that a Good assessment is carried out and that the requirements for prompt notification are met.

##### 8.2.2.2.1. Notices obtained during non-interference surveys

Distinguish between research projects based on data collected in the course of non-interventional trial by collecting primary data directly from patients and health workers, and research projects based on secondary use of data such as medical card or health system electronic records, systematic reviews or meta-analyzes. should be carried out.

The notification shall be drawn up by the licensee or the declarant if there is at least a possible cause-and-effect relationship with the suspected medicine; Notices of adverse events in which the cause-and-effect relationship is considered suspicious should be included in the final report on the investigation.

Notices of additional effects suspected of having at least a possible cause-and-effect relationship with the suspected medicine should be provided to the person or licensee who reports the non-interventional trial, which is conducted by collecting

initial data directly from patients or health care providers. Researchers should submit to the Institution, if appropriate, notifications of other suspicious side effects related to the medicine being studied but not interacting with the medicine (s) being studied.

Non-interference studies based on secondary data use do not require notification of identified side effects. All information on identified side effects is summarized in the final research report.

The requirements for the issuance of notices of additional effects in case of doubt of the holder of the license should be clarified with the Authority.

The licensee must always comply with applicable national law on the submission of notices of suspected side effects to local ethics commissions and researchers.

8.2.2.2.2. The program of use of the medicine for humanitarian purposes in exceptional cases, the program of individual use of the unregistered medicine.

If the holder of the license or the medical professional is aware and identifies suspicious side effects during the implementation of the program of emergency use of the medicine for humanitarian purposes or the program of individual use of the unregistered medicine, notifications of such suspicious side effects are provided as follows.

When an additional effect is identified during an active search, it should be provided by the original source or licensee only if the cause-and-effect relationship with the use of the suspected medicine is at least as possible. They should be considered as notifications of side effects obtained on demand.

If an adverse effect has not been identified on the basis of an active search / demand, all adverse and unintentional adverse reactions to the medicinal product should be considered as a notification of suspected undesirable side effects and the notification should be provided accordingly.

8.2.2.2.3. Patient support program

The patient support program is an organized data collection scheme in which the licensee collects information on the use of the medicine. These include patient and disease monitoring post-registration support programs, patient monitoring, collection of patient compliance data, and monitoring through compensation systems.

It is possible to actively search for additional effects when performing various types of organized data collection; in which case they shall be treated as notifications received on demand. Only the reporting person or the cardholder should report at least the possible side effects that are suspected to have an additional effect.

Unless an additional effect is identified on the basis of an active search / demand within an organized data collection system, all adverse effects on medicinal products reported to the licensee by the healthcare professional or patient should be treated as notifications of suspected side effects and the notification should be provided accordingly.

#### 8.2.2.3. Notices published in scientific and medical literature

Licensees are required by law to monitor publications published in the scientific and medical literature in all countries where the use of relevant medicines is permitted, in compliance with the requirements for notification of side effects.

Notices (information) of the following side effects identified during the monitoring of publications in the scientific and medical literature are not reported immediately:

- possession may be excluded on the basis of the active ingredient, composition, method of administration, country of primary source or country of origin of the suspected additional effect;
- literature articles that in themselves constitute generalized analysis of data from public databases or describe information about patients in the form of tables or series of lists. This type of literature describes the side effects of a group of patients taking a particular medicine in order to identify or quantify the safety risks associated with the medicine. The articles presented are often related to pharmacoepidemiological studies, the main purpose of which is to identify / assess the risks that may affect the overall benefit-risk ratio of the medicine.

The safety information provided in such articles should be reviewed in the relevant sections of the PSUR and taken into account in the analysis of the effect of the medicine on the benefit-risk ratio. In addition, the Authority should be notified immediately of new safety information that may affect the benefit-risk ratio of the medicinal product.

#### 8.2.2.4. Suspicious side effects associated with poor quality or counterfeit medications

Notices of suspected side effects should be made in the case of suspected or approved, counterfeit or substandard medicines, if they relate to validated notices.

In such cases, urgent measures may be required to protect public health, such as the withdrawal of one or more defective batches (s) of a medicine from the pharmaceutical market. Licensees must have a system in place to ensure that notices of suspected side effects obtained from counterfeit or defective medicines are immediately evaluated and investigated. If the defect is confirmed, the immediate manufacturer and the Authority must be notified immediately.

#### 8.2.2.5. Suspicion of medicine transmission of an infectious agent

Any pathogenic or non-pathogenic microorganism, virus, or infectious particle (eg, a prion, a protein that transmits transmissible sponge-like encephalopathy) is considered an infectious agent.

Suspicion of medicine transmission of infectious agents is considered a serious side effect that must be reported immediately in accordance with the requirements of national legislation. This requirement also applies to vaccines.

Suspicion of transmission of an infectious agent, clinical signs or symptoms indicating the presence of infection in a patient exposed to the medicine, can be confirmed on the basis of laboratory results. Particular attention should be paid to

the detection of known infections / pathogens that are potentially transmitted through the medicine, but the risk of the presence of unknown pathogens should also be considered.

Care should be taken in the context of assessing the suspicion of medicine transmission of an infectious agent and, if possible, the source of infection (eg, contamination), cause (eg, injection or ingestion), and the patient's clinical condition (immunosuppressive condition or prior vaccination) ) should be differentiated between.

Confirmation of suspected medicine contamination (including inappropriate inactivation or attenuation of the virulence of infectious agents as active ingredients) reinforces evidence of transmission and quality defect of the infectious agent.

8.2.2.6. The period between the submission of the application for state registration and the issuance of a state registration certificate

During the period between the submission of the application for state registration and the issuance of the state registration card, the cardholder may receive information that may affect the benefit-risk ratio of the medicinal product. It is the responsibility of the licensee to ensure that this information is provided to the Institution.

8.2.2.7. Period after suspension or cancellation of state registration

The holder of the license must continue to report any suspicious side effects associated with the medicinal product in the period after the termination of the state registration card, provided that it meets the criteria for urgent notification.

In case of revocation of the state registration card, the cardholder should be encouraged to continue collecting information on suspicious side effects for purposes such as delaying side effects or mitigation of assessment in the event of retrospective side effects.

8.2.2.8. Period during a health emergency

A health emergency is a threat to public health that has been duly recognized by the World Health Organization (WHO). It is possible to amend the requirements for regular reporting in the event of a health emergency.

8.2.2.9. Notices on the basis of lawsuits in relation to medicines

In the case of medicinal products, the handling of notices arising from the outcome of lawsuits must be conducted in the same manner as for notices obtained without request. The notification should only be submitted by the licensee or the declarant if there is at least a possible cause-and-effect relationship with the suspected medicine. In such cases, immediate notification shall be carried out if the criteria established by the legislation are met.

8.3. Preparation of ICSR

8.3.1. Information on suspicious, interacting, and concomitant medications

Notices of side effects should indicate the dosage regimen of suspected, interacting, and / or concomitant medications and the start and end dates of

treatment. Each active ingredient should be indicated separately for combination medicines containing more than one active ingredient.

When it is stated that the described side effect is related only to the therapeutic class, it is considered incomplete and does not meet the criteria for immediate notification of the side effect. Efforts should be made to obtain missing information about the suspected medicine and further action should be taken in case of side effects.

#### 8.3.2. Description of side effects and assessment of cause-and-effect relationship

For each individual event, all available information on the additional impact is provided. The information should be presented in a logical chronological order, including a chronology of changes in the patient's condition, including clinical course, therapeutic measures, outcome, and subsequent information obtained. The description contains all known clinical and related information (laboratory, diagnostic, etc.), including the patient's characteristics, treatment details, medical history, clinical course of symptoms (s), diagnosis, side effects and their outcomes, important laboratory information and suspicious appendix there should be a comprehensive, independent "medical report" containing any other information that confirms or denies the effects. Where applicable, important information on autopsy or post-mortem examination should be summarized.

If the primary source (informant) provides additional information in addition to the assessment of the cause-and-effect relationship, the Authority and the licensees may add their own explanation of the cause-and-effect relationship between the suspected medicine (s) and the side effects (s).

#### 8.3.3. Results of analyzes and instrumental research

Side effects should include the results of procedures and tests performed to diagnose or confirm the reaction / event, including non-medicine-related causes (eg, serological tests for infectious hepatitis if medicine-induced hepatitis is suspected). Both positive and negative research findings should be reported.

#### 8.3.4. Next information

Subsequent information on side effects should be sent to the sender of the side effects notification immediately if important new medical information is obtained. Important new information refers to any new information or data, such as new suspicious side effects (s), changes in the assessment of the cause-and-effect relationship, and changes in the initial (previous) information about the event that affect the medical assessment of the event. A medical opinion is always required to identify important new information that needs to be reported urgently.

There are also cases where the severity criteria and / or the assessment of the cause-and-effect relationship in individual cases are reduced (eg, subsequent information causes the severity criteria to change from a serious side effect to a non-serious one; the cause-and-effect relationship assessment is questionable. communication), should be considered as significant changes and information

should be provided in accordance with the requirements for the urgent provision of information.

Subsequent information should not be provided immediately when it results in minor changes to the initial data and assessment. For example, insignificant changes in some dates without affecting the assessment or transmission of the event, or corrections to typographical errors in the original version of the event, are insignificant changes. However, in some cases, when a formal assessment is insufficient (for example, a change in the date of birth constitutes a significant change in the patient's age), a medical expert's opinion should be sought as to the significance of the subsequent information.

#### 8.3.5. Cancellation of events

A canceled event is an event that should no longer be considered in valuation procedures. Cancellation is made when the event is found to be completely wrong or the reports are repeated. The cancellation of the event is carried out by informing the sender of the event that the event is no longer considered valid. However, the notification must be kept in the pharmacovigilance database of the sender.

### **8.4. Cooperation with the World Health Organization**

Ensures that notices of suspected adverse effects against medicinal products identified in the territory of the World Health Organization are regularly submitted to the World Health Organization's Medicines Monitoring Center for inclusion in the WHO database on side effects.

## **9. Periodically updated security report (PSUR)**

PSUR is a pharmacovigilance document, the purpose of which is to provide the licensee with the results of the assessment of the benefit-risk ratio of the medicine at certain stages of the post-registration period.

The agency should conduct an assessment of PSUR by identifying possible new risks and their impact on the assessment of the benefit-risk ratio of the medicine. Based on the results of the assessment, the Agency determines the need for further research / testing of the safety or efficacy of the medicine, regulatory action depending on the registration status of the medicine, or changes in the medicine's instructions to ensure its use if the benefits outweigh the risks.

### 9.1. Objectives of PSUR

9.1.1. The main purpose of PSUR is to provide a detailed and critical analysis of the benefit-risk ratio of the medicine, taking into account all new safety data and their cumulative effect on the safety profile and effectiveness of the medicine. PSUR is a tool for post-registration assessment of the benefit-risk ratio of the medicine at certain stages of the medicine life cycle.

9.1.2. Based on the assessment of newly identified safety data in the post-registration application process, the licensee should regularly analyze the impact of

new data on the benefit-risk ratio, re-evaluate this indicator, as well as benefit through effective risk management and mitigation measures. The need to optimize the risk ratio must be identified.

## **9.2. Principles of risk-benefit assessment in PSUR**

The assessment of the benefit-risk ratio is continuous throughout the life cycle of the medicine in order to ensure the protection of public health and improve the safety of patients through the implementation of effective risk minimization measures. The basis for the analysis is the information on safety and effectiveness collected during the relevant periods that make up the reporting periods. The assessment includes the following stages:

1. Critical analysis of all safety data obtained during the reporting period, identifying possible new signals that have been identified, indicating the completion of existing knowledge on new potential or identified risks, or previously identified risks;
2. Critical summarization of all information obtained during the reporting period on the safety and efficacy of the medicinal product (both in clinical trials / trials and in medical practice), with an assessment of the effect of the medicinal product on the benefit-risk ratio;
3. Carrying out an integrated benefit-risk analysis based on all available cumulative data from the date of first registration in any country / from the date of first registration for non-intervention clinical trials in any country;
4. Summarize information on feasible or planned risk mitigation measures;
5. Identify signals or risks and / or offer and plan additional pharmacovigilance activities.

## **9.3. Principles of preparation of PSUR**

The holder of the license must prepare a single PSUR for all its medicinal products, containing the same active ingredient or the same combination of active ingredients according to all approved instructions, methods of administration, dosage forms and dosage regimens. In specific cases, information on separate instructions, dosage forms, injection methods or dosing regimens may be required to be provided in a separate section of this report, with appropriate reflection of aspects of the safety profile, without the preparation of a separate PSUR. In exceptional cases, for example, in the case of a different form of release with completely different indications for medical use, the development of a separate PSUR may be justified.

## **9.4. The composition of PSUR**

9.4.1. The periodically updated security report should contain cumulative information obtained during the reporting period, which tends to be new from the date of registration. Cumulative information is considered when conducting an overall safety assessment and an integrated benefit-risk assessment.

The PSUR should include aggregated information on all sources of acquisition of significant information on efficiency and safety that should be taken into account during the next assessment of the benefit-risk ratio and available to the licensee. The mentioned information consists of the following:

a) generalized information on the results of medical use

- spontaneous notification information;
- medical literature information;
- information obtained in the course of active monitoring methods (for example, analysis of internal or external databases);
- security signals inspected by the license holder;
- information received from distribution or marketing partners;

b) generalized information on clinical trials / trials:

- ongoing clinical studies / trials or other studies / trials conducted by the licensee or his / her representative or studies / trials completed during the reporting period;
- therapeutic application of the studied medicine;
- observational or epidemiological studies;
- research on medicine use assessment;
- Preclinical studies (toxicological and in vitro studies);
- clinical trials performed by the licensee's partners on the development or marketing of the medicinal product;
- clinical trials in which the therapeutic effect of the medicine is found to be insufficient, which may affect the benefit-risk ratio;

c) generalized information from other sources:

- information obtained from other sources related to the assessment of the effectiveness or safety of medicines belonging to a similar pharmacotherapeutic group;
- reports on the safety of other PSUR or the medicinal product being prepared (for example, contracted partners or research initiators);
- Important information obtained after the completion of the PSUR.

9.4.2. PSUR should include the following sections:

Part I. Signed title sheet

Part II. Summary of the main content

Part III. Table of contents of the report:

1. Introduction
2. Worldwide registration status
3. Measures taken in connection with security information during the reporting period
4. Changes in the reference safety information of the medicinal product
5. Estimation of the number of patients exposed to the medicine
5.1. The total number of patients affected in clinical trials

5.2. Total number of affected patients according to market application data
6. Generalized table information
6.1. Reference information
6.2. An overview of the serious side effects found in clinical trials
6.3. Summary information on post-registration usage information
7. Summary of important data obtained during clinical trials during the reporting period
7.1. Completed clinical trials
7.2. Ongoing clinical trials
7.3. Subsequent long-term monitoring
7.4. Other therapeutic use of the medicine
7.5. New safety information regarding the determination of fixed combinations
8. Data from non-interference studies
9. Data from other clinical trials and other sources
10. Data from pre-clinical studies
11. Literature
12. Other periodic reports
13. Insufficient therapeutic efficacy in controlled clinical trials
14. Important information obtained after the completion of the PSUR
15. Review of signals: new, ongoing and closed
16. Signals and risk assessment
16.1. Review of security issues
16.2. Signal evaluation
16.3. Risk and new information assessment
16.4. Risk characteristics
16.5. Effectiveness of risk minimization measures (if appropriate)
17. Benefit assessment
17.1. Important key information on efficacy in clinical trials and application in medical practice
17.2. New information on efficacy in clinical trials and medical practice
17.3. Characteristics of benefits
18. Integrated analysis of benefit-risk ratio according to approved guidelines
18.1. The context of the benefit-risk ratio - medical needs and important alternatives
18.2. Evaluation of the benefit-risk ratio analysis procedure
19. Results and measures
20. Annexes to PSUR

#### 9.4.3. Title page

The title page contains the report number (reports should be numbered sequentially), the name of the medicine, the international date of birth, the reporting period (or extraordinary application procedure at the request of the Agency), the date of the report, information about the license holder and confidentiality of information notes should be shown. The title page must be signed.

#### 9.4.4. Summary of the main content

The purpose of summarizing the content is to provide a summary of the content and relatively important information that makes up the PSUR. This section should contain the following information:

- introduction, report number and reporting period;
- name of the medicine, pharmacotherapeutic class, mechanism of action, instructions for use, dosage form, dose, method of injection;
- assessment of cumulative impact in the course of clinical trials;
- post-registration usage interval and cumulative impact assessment during this period;
- number of countries in the territory of which the use of the medicine is allowed;
- generalized information on the assessment of the benefit-risk ratio;
- measures taken and proposed in relation to aspects of the safety profile, including significant changes to the researcher's brochure during the clinical trial phase and to the post-registration instructions, or other risk mitigation measures;
- results.

9.4.5. The summary section of the report should be accompanied by a table of contents of the PSUR.

### **9.5. Requirements for the content of each part of the PSUR**

#### 9.5.1. "Introduction" section of PSUR

The introduction must contain the following information:

- international date of birth, reporting period and report sequence number;
- name of the medicine, pharmacotherapeutic class, mechanism of action, instructions for use, dosage form, dose, method of injection;
- a brief description of the populations treated with the medicine or included in clinical trials.
- A brief description and explanation of any information related to the information required in the PSUR.

#### 9.5.2. PSUR's "Global Registration Status" section

This section of the PSUR should provide a brief summary of the initial registration dates in the countries of the world, approved instructions for use, registered forms and dosages, indicating the existing records as of the date of preparation of the PSUR.

### 9.5.3. PSUR section "Measures taken in connection with security information during the reporting period"

The section describes the significant actions taken during the reporting period in relation to both ongoing clinical trials / trials and post-registration use by the competent authorities, licensees, clinical research sponsor / applicant, data monitoring / evaluation committee and ethics commission, based on the safety information below. :

- information that significantly affected the benefit-risk ratio of the registered medicine; and / or
- information that influenced the conduct of a specific clinical study (s) or the clinical development program of the medicine as a whole.

The grounds for the implementation of the measures given in the section and, if necessary, additional information (if available) should be provided.

1. Measures taken in relation to the medicine under study may include:

- a) refusal to authorize clinical trials / trials due to safety concerns or ethical issues;
- temporary partial or complete cessation of clinical trials / trials or early cessation of clinical trials / trials due to safety data or insufficient therapeutic efficacy;
- recall of the researched medicine or comparative medicine;
- Refusal to obtain a permit for use in accordance with the instructions investigated during the clinical trial, including the voluntary withdrawal of the application for registration;
- application of risk minimization measures, including:
  - changes to the research / test protocol due to safety or efficacy data (such as changes in dosage regimen, changes in inclusion / exclusion criteria, application of additional measures to monitor research subjects, limitation of duration of research / testing);
  - Restriction of the population under study or indications for use;
  - making changes to the informed agreement in connection with aspects of the security profile;
  - making changes in the composition;
  - additional requirements of the competent authorities for the provision of information on the safety of medicines in a special way;
  - special informing of doctors-researchers or medical workers;
  - planning of new research to assess aspects of the security profile.

2. The measures taken in connection with the registered medicine are as follows:

- suspension or revocation of the registration card;
- implementation of risk minimization plan, including:
  - significant restrictions on the application or distribution of other risk mitigation measures;
  - Significant changes in the instructions for use, which may affect the development program, including the restriction of the group of patients to whom the medicine is prescribed or prescribed;

- special informing of medical staff;
  - Requirement for post-registration research by the competent authorities.
- 9.5.4. PSUR section "Changes in the reference safety information of the medicine" section

This section lists information on all significant changes made to the reference safety information of the medicinal product during the reporting period. These significant changes include contraindications, precautions, changes to specific indication sections, serious side effects, side effects of particular interest, information on interaction reactions, data from ongoing and completed clinical trials / trials, important information from pre-clinical studies (e.g. study of carcinogenicity). Information on the changes should be provided in the relevant sections of the PSUR. In addition to the PSUR, the version of the reference safety information of the medicinal product must be attached together with the relevant changes.

The licensee also provides information on changes made to the operating instructions or in the process of inclusion in accordance with the updated version of the licensee's basic security information, provided in the appendix.

9.5.5. PSUR section "Estimation of the number of patients exposed to the medicine" section

PSUR should include an accurate estimate of the number of patients affected by the medicine, as well as information on sales volume and the number of appointments. This assessment should be accompanied by a qualitative and quantitative analysis of the application in real medical practice, based on all available information for the licensee and the results of observational studies to assess the use of the medicine, indicating how it may differ from the approved application.

This section should provide an estimate of the size and characteristics of the population affected by the medicine, as well as a brief description of the method used for the assessment and the shortcomings of this method.

Adequate methods for assessing the effect on the subject / patient should be used in all sections of the PSUR for a single medicine. If it is deemed appropriate to substitute the valuation method used, both methods and their calculations should be submitted to the PSUR with clarification of the substitution.

9.5.5.1. PSUR subsection "Total number of patients affected in clinical trials"

This section of the PSUR should include the following information on patients included in clinical trials / trials (table format recommended):

- the cumulative number of subjects who were included in ongoing and completed clinical trials / trials and who have been exposed to the medicine, placebo and / or active medicine since the first international study date of the developed medicine. It may be acceptable that detailed information is not available in relation to medicines that have been in circulation for a long time;

- more detailed cumulative information on the affected research subjects, if available (for example, grouped by age, sex, heredity according to the entire development program);
- significant differences between studies / trials in terms of prescribed doses, route of administration, and subgroups;
- if clinical studies / trials have been performed on specific groups of patients (eg pregnant women, patients with impaired renal, hepatic or cardiovascular function; patients with clinically significant genetic polymorphisms);
- In the event of significant differences in exposure time between randomly selected patients to receive the medicine or reference medicine (s) being studied, or discrepancies in duration of exposure between clinical trials / trials, the impact assessment should be subject-time (patient-days), -months, or -years);
- Data on the effect of the medicine under study in healthy volunteers may be of little importance for assessing the safety profile of the medicine as a whole, depending on the type of side effects observed, especially if patients are exposed to a single dose. Detailed information should be provided with an explanation if necessary;
- If the generalized information on side effects found during clinical trials / trials has a significant additional effect, the patient should be informed of the impact assessment, if possible;
- Demographic characteristics of patients related to a specific clinical trial / trial should be presented separately.

#### 9.5.5.2. PSUR sub-section “Total number of affected patients according to market application data”

Where possible, a separate impact assessment should be provided for the cumulative effect (from the international date of birth) and at certain intervals (from the date of the previous PSUR data lock). The unit should provide an assessment of the number of affected patients, as well as the method (s) in which the identification and assessment is performed. If it is not possible to estimate the number of affected patients, a justification must be provided. If it is not possible to estimate the number of patients, alternative assessment options should be provided, indicating the method (s) to be performed. The patient-day indicator and the number of appointments are examples of alternative indicators of impact assessment. Only when these indicators are not available can sales volume estimates expressed in units of mass or doses be used. The prescribed daily dose concept can be applied to patients to obtain data on the effect.

The information must be submitted in the following categories:

##### 1. Post-registration use (pre-clinical studies / trials):

An overall assessment should be provided. Where appropriate, additional information should be provided by gender, age, indications, dosage, dosage forms, and distribution by region. Other variables depending on the medicine, such as the

number of vaccinations administered, the method of injection, and the duration of treatment, may be significant.

When a series of notifications of additional effects indicating the probability of the presence of a signal are identified, information on the effects should be provided within the relevant subgroup, if possible.

## 2. Post-registration use in special population groups:

If the medicine is used in specific population groups at the post-registration stage, the available information and the calculation method used should be provided, depending on the number of patients affected. Sources of this data may include non-interference surveys, including registers, designed to obtain data directly on specific population subgroups.

The populations included in the data assessment in this section include, but are not limited to:

- pediatric population;
- elderly population;
- women during pregnancy and lactation;
- patients with hepatic and / or renal impairment;
- Patients with other important side pathologies;
- patients whose disease severity differs from the level studied in the course of clinical trials;
- sub-population with carriers of genetic polymorphism (s);
- Patients of other hereditary or ethnic backgrounds.

## 3. Features of use of the medicine

When the holder of the card is informed about the specific features of the application of the medicinal product, a description of these features should be provided, and an appropriate assessment and explanation of the safety information should be provided. Such features include, in particular, overdose, malicious use, abuse and use outside of the guidelines approved in medical practice. If relevant information is available, the licensee may comment on the extent to which the application is supported by clinical protocols, the evidence base of clinical trials, or the general lack of registered alternatives. Where relevant information is available, a quantitative assessment of the scope of the application should be provided.

### 9.5.6. "Generalized table data" section of PSUR

The purpose of this section of the PSUR is to present information on side effects / adverse events identified during clinical trials / trials in the form of aggregated tabular data. At the discretion of the cardholder, a graphical description of certain aspects of the information may be provided for easy understanding.

The classification of significant adverse effects in the aggregate table data should be consistent with the classification of additional effects notices using the severity criteria established by law, based on the results of the assessment. The inclusion of serious side effects in the summary table data of the Notice of Side Effects (SID) should be in accordance with the severity criteria set out in the Pharmacovigilance

Regulations for Medicinal Products. The assessment of severity should not change during the preparation of the data for inclusion in the PSUR.

#### 9.5.6.1. PSUR sub-section "Reference information"

This subsection shows the version of the Medical Terminology Dictionary (MedDRA) used for the analysis of side effects / adverse events.

#### 9.5.6.2. PSUR subsection "Summary information on serious side effects identified during clinical trials / trials"

Substantiation of the appendix containing summary table information on serious adverse events identified during the clinical trials / trials conducted by the licensee from the date of the first international study of the medicine developed in this subsection of the PSUR to the date of the current periodically updated safety report. should be given. All information excluded by the cardholder (for example, information on clinical trial / trial results may not be available for several years) must be explained. The data in tabular form should be grouped according to the classification of side effects by organ-system classes relative to the medicine under study, as well as comparative medicines (active and placebo). Where appropriate, data should be presented in a grouped form for clinical trials / trials, indications, routes of administration, and other variables.

The following aspects should be considered.

It is recommended that a cause-and-effect assessment of rare side effects be provided. For the possibility of group (including frequency) comparisons, information on all serious adverse events, both for the medicine under study and for placebo and comparison medicines, should be provided. It is useful to provide information on the relationship between the prescribed dose and frequency.

The summary table should include data on serious adverse events in blind and open clinical trials. Open data may be provided based on the results of completed clinical trials and on individual cases where the blind method has been eliminated for certain reasons, such as safety concerns or compliance with immediate notification requirements. Clinical research / trial sponsors / applicants and licensees do not disclose the results of blind research directly related to the development of PSUR.

Certain additional effects may be excluded from the summary, but all such deductions must be substantiated in the report. For example, additional effects identified in the protocol as excluded from the immediate notification procedure due to their specificity in the target population or coinciding with the endpoints of the clinical study and included only in the general database.

#### 9.5.6.3. Sub-section "Summary information on post-registration usage data" of PSUR

This section of the PSUR provides a rationale for the appendix, which contains aggregated data in the form of a table on the cumulative side effects for the reporting period and the entire period from the international date of birth of the medicine to the date of the lock. This section includes information on side effects

obtained during non-interventional studies and spontaneous notifications, including information from medical and pharmaceutical workers, consumers, patients, authorities, and information published in the medical literature. Serious and non-serious side effects should be presented in separate tables. The information in the table should be divided according to the classification of organ-functional class. Separate tables of additional effects can be provided by grouping information on specific important aspects of the safety profile according to instructions, method of injection and other parameters.

9.5.7. "Summary of important data obtained during clinical trials / trials" during the reporting period

In addition, the licensee should list interventional clinical trials organized to quantify, characterize and identify the level of risk, confirm the safety profile of the medicinal product, or evaluate the effectiveness of risk mitigation measures completed or ongoing during the reporting period.

Where possible, data should be categorized by gender and age (especially in the elderly compared to the pediatric population), indications, dosing regimens, and region.

Signals detected during clinical trials should be presented in tabular form in Section 15 of the PSUR (overview of signals: new, ongoing or closed). The signals are evaluated to determine whether the signals are potential or an identified risk; The risk should be assessed and characterized in Section 16.3 ("Risk and New Data Assessment") and Section 16.4 ("Risk Characteristics") of the PSUR, respectively.

This section of the PSUR should provide summary information on clinically relevant efficacy and safety data obtained from the following sources during the reporting period:

9.5.7.1. "Completed clinical trials" subsection of PSUR

This sub-section of the PSUR should provide a summary of clinically relevant data on efficacy and safety obtained from clinical trials / trials completed during the reporting period. This information should be presented in a concise or summary form. It may contain information that confirms or denies previously identified security signals, as well as evidence of new security signals.

9.5.7.2. PSUR subsection "Ongoing clinical trials / trials"

If any clinically relevant information obtained during ongoing clinical trials / trials is known to the holder (for example, in the course of an intermediate safety analysis or in the elimination of a blind approach to serious adverse events), this section summarizes new safety information should be informed. This section may also contain information that confirms or denies previously identified security signals, as well as evidence of new security signals.

9.5.7.3. PSUR sub-section "Subsequent long-term monitoring"

Where available long-term follow-up data from patients included in clinical trials / trials are available, this subsection contains information relevant to the safety profile obtained from subsequent long-term follow-up.

#### 9.5.7.4. Subsection "Other therapeutic use of medicines" of PSUR

This subsection of the PSUR should contain clinically relevant information on security obtained from other programs performed by the licensee under special protocols (eg extended access programs, compassion, personal access, and other exceptional use programs).

#### 9.5.7.5. PSUR subsection "New safety information in relation to the determination of fixed combinations"

Unless otherwise specified by the institution, the following information should be provided regarding the combined treatment:

a) Where a medicine is approved for use as a component of a stable medicine treatment or as a component of a multicomponent treatment regimen, the subsection should summarize important information on the safety of combination therapy.

b) If the medicinal product is a combination medicinal product, this subsection shall summarize the important safety information for each of the individual components.

#### 9.5.8. "Data from non-interference research" section of PSUR

This section provides information on relevant safety information available during the reporting period or their impact on risk-benefit assessment, obtained from the results of non-intervention clinical trials / trials organized by the licensee (eg observational studies, epidemiological studies, registers, active monitoring programs). the data are summarized. The section should contain information related to aspects of the safety profile obtained from the results of studies evaluating the use of the medicine.

In addition to the report, the license holder shall identify, characterize and quantify aspects of the safety profile that require caution, approve the safety profile of the medicinal product, or evaluate the effectiveness of risk mitigation measures implemented or in progress during the reporting period (eg post-registration). safety studies).

The implementation phase report or reports prepared during the reporting period should be included in the PSUR appendix.

#### 9.5.9. PSUR section "Information from other clinical trials and other sources"

This section provides information on the benefit-risk ratio of the medicine obtained from other sources available to the licensee during the reporting period, or on the results of other clinical trials (for example, the results of meta-analyzes of randomized clinical trials, medicine development). partners' safety information, etc.) should be summarized.

#### 9.5.10. "Pre-clinical research data" section of PSUR

This section provides summary information on safety data that is relevant to the safety profile, based on the results of in-vivo and in vitro pre-clinical studies (eg, carcinogenicity, reproductive toxicity, or immunotoxicity) performed during or completed during the reporting period. An assessment of the impact of the data obtained on the safety profile should be provided in Section 16 (“Alarm and Risk Assessment”) and Section 18 (“Integrated Risk-Risk Analysis of Approved Indications”).

#### 9.5.11. "Literature" section of PSUR

The section summarizes new and important safety information obtained from unpublished monographs published in the scientific literature that has undergone expert evaluation, or that are related to the medicine and are available to the licensee during the reporting period.

The search for literature for the development of PSUR should be broader than the search for side effects notifications (ICSR), as it should also include studies in which the results were evaluated in terms of safety in the study subject groups.

Specific aspects of the security profile that should be included in the search, but which may not be detected during individual events in order to obtain information on additional effects, include:

- pregnancy consequences not accompanied by undesirable consequences (including incomplete termination);
- use in the pediatric population;
- application for use programs in exceptional circumstances for the sake of mercy, application for individual destination programs;
- lack of efficiency;
- asymptomatic overdose, inappropriate and improper use;
- medical errors that are not accompanied by the development of adverse events;
- Important results of pre-clinical research.

Where appropriate, information on other asset items in this group should be considered.

#### 9.5.12. Other periodic reports

This section of the PSUR is valid only in the case of a fixed combination, as well as in the case of a medicine with a number of instructions and / or dosage forms, in specific cases where more than one PSUR is prepared by the licensee in agreement with the competent authorities.

In general, the licensee prepares a PSUR related to an active substance (except in cases where there are other requirements by the Institution); If more than one PSUR is prepared for one medicinal product, significant safety information from the other PSUR should be summarized in this section, unless otherwise provided in the other sections of the given PSUR.

Where available, under the agreement, the licensee must provide a summary of the significant safety information provided to the PSUR by other parties (eg sponsors or other partners) during the reporting period.

#### 9.5.13. “Insufficient therapeutic efficacy in controlled clinical trials” section of PSUR

Data from clinical trials that indicate insufficient therapeutic efficacy or insufficient therapeutic efficacy in relation to the medicines used to treat and prevent serious and life-threatening diseases may indicate a significant risk to the target population; this information should be analyzed and summarized in a given section of the PSUR.

Data from clinical trials demonstrating the ineffectiveness of medicines not intended for the treatment of vital pathologies should also be analyzed in this section of the PSUR, if appropriate, to assess the benefit-risk ratio.

#### 9.5.14. PSUR section "Important information obtained after the completion of the PSUR" section

This section summarizes the potentially important information on safety and effectiveness obtained after the data lock point but during the preparation of the PSUR. The data of new publications of clinical significance, important data of further observation, clinically important toxicological data, as well as all activities of the licensee, data evaluation committees on aspects of the safety profile of the competent authorities are exemplary. Notices of new side effects should not be included in the section, unless they constitute an important characteristic event or an important safety signal (for example, the first case of an important adverse event).

The information in the section should be taken into account when assessing risk and new information.

#### 9.5.15. PSUR's "Signal Review: New, Ongoing, and Closed" section

The purpose of this section is to provide a detailed overview of detected signals, signals under evaluation and signals not evaluated during the reporting period.

The cardholder must provide a brief description of the method used to detect the signals, as well as information sources for the detection of the signals.

Newly detected signals include signals detected during the reporting period. The signals under review include signals that are in the evaluation phase for the data lock point. Closed signals include signals that have been evaluated during the reporting period. For the reporting period, both new and closed signals should be included in the closed signals section.

The section should contain information in the form of a table on related signals reviewed during the reporting period. The table is attached to the report in the form of an attachment. At the discretion of the cardholder, this information may also include cumulative information on the signals, including previously connected signals, indicating the date on which the generalization of the signals has begun.

Detailed signal assessments are included in Sections 16.2 (“Alarm Assessment”) and 16.3 (“Risk and New Information Assessment”) of the PSUR.

#### 9.5.16. "Signals and risk assessment" section of PSUR

##### 9.5.16.1. PSUR sub-section "Review of security problems"

The purpose of the subsection is to provide a summary of key information on important aspects of the security profile, indicating what new information can be provided on each security issue and what aspects can be assessed. The following factors should be considered when determining the importance of each risk aspect:

- the severity of the risk from a medical point of view, including the impact on the individual condition of patients;
- frequency, predictability, predictability and reversibility;
- potential impact on public health (frequency of occurrence in the population; size of the affected population);
- public acceptance of risk if possible impact on public health (eg refusal of vaccination program).

The generalized information should provide the PSUR with available information on the medicinal product from the beginning of the reporting period and reflect the following:

- significant identified risks;
- significant potential risks;
- important missing information.

With respect to medicines with a safety specification, the information included in this subsection should coincide with the summary information provided in the current version of the safety specification for the reporting period of the PSUR.

With regard to medicines that do not have a safety specification, the subsection should provide important identifiable, potential risks and significant missing information on the use of the medicine based on pre- and post-registration data. Examples may include the following information:

- important side effects;
- interaction with other medicines;
- medical errors or omissions detected in cases not accompanied by the development of side effects;
- interaction with food or other substances;
- the consequences of exposure to occupational medicines;
- Pharmacological effects by class.

The generalization of relevant critical missing information should assess the criticality of gaps in existing knowledge on certain aspects of the safety profile relative to target populations.

#### 9.5.16.2. PSUR's "Signal Evaluation" subsection

The information presented in the subsection should summarize the results of the assessment of security signals completed during the reporting period; There are two main categories:

1. Signals that may fall into the category of potential or identified risks based on the results of the assessment, including the lack of therapeutic efficacy. These related signals are considered in Section 16.3 (“Risk and New Information Assessment”) of the PSUR.

2. Signals rejected as false alarms according to the results of the assessment, based on a scientific assessment of the information available at the time of the assessment procedure. With respect to this category of signals, a description must be provided to justify the rejection of each signal from the signal category. This description may be included in the main text of the PSUR or in its appendix.

For the reporting period, it is recommended that a correlation be made between the amount and details of the signal assessment data and the importance of a given aspect of the safety profile for public health, as well as the adequacy of the evidence base. This information should include the following aspects:

- instantaneous moment for the source or generation of the signal;
- substantiation related to the assessment;
- evaluation methods, including data sources, search criteria or analytical approaches;
- results: generalized information on critical analysis of the data considered during signal evaluation;
- discussion;
- feedback, including proposed activities.

#### 9.5.16.3. PSUR sub-section "Risk and new information assessment"

The cardholder must provide a critical assessment of the new information for the reporting period in relation to new or previously identified risks (important or otherwise).

This subsection of the PSUR should include a description and assessment of all risks identified during the reporting period, as well as an assessment of the impact of new information on previously identified risks. Generalized or repetitive information included in other sections of the SLP is not included in this section, but comments on the new information and its assessment are provided depending on the characteristics of the risk profile.

New information should be provided in the following sections:

- new potential risks;
- newly identified risks;
- new information on previously identified risks (potential and identified);
- Update on important missing information.

A brief description of the important risks is provided. The level of detail for risks for which new information was obtained during the reporting period, related to 'other' and not related to 'important', should be consistent with the given risk database and the significance of its impact on public health.

All new information on the effect of a medicine on the population, or information on previously missing information, should be critically evaluated. Indicates which aspects of the security profile that pose a threat, as well as which aspects of the security profile that are not clear, remain unclear.

#### 9.5.16.4. PSUR subsection "Risk characteristics"

The subsection provides a description of significant identified risks and significant potential risks (including those not limited to the reporting period) based on cumulative data and describes important missing information.

Where appropriate, risk information should include, taking into account the source of the information:

- speed;
- number of detected cases; accuracy of assessment taking into account the source of data;
- number of patients, sick months (years), etc. volume of destination expressed as; accuracy of assessment;
- relative risk assessment and assessment accuracy;
- absolute risk assessment and accuracy of assessment;
- effect on the patient (effect on symptoms, quality of life);
- impact on public health;
- risk factors (eg individual risk factors (age, pregnancy / lactation, liver / kidney dysfunction, significant co-morbidities, disease severity, genetic polymorphism, race and / or ethnicity), dose);
- duration of treatment, risk period;
- preventability (predictability, the ability to monitor the situation based on indicative symptoms or laboratory parameters);
- reversibility;
- potential mechanism;
- level of evidence and uncertainty, including analysis of conflicting facts when they exist.

In the case of significant differences between the identified and potential risks identified in the preparation of PSUR for medicines with multiple indications, dosage forms or injection methods, it may be justified to provide risk information separately for indications, dosage forms or injection methods. The following sections can be submitted:

- risks specific to the active substance;
- risks specific to certain forms of release or injection methods (including exposure to occupational medicines);
- risks specific to specific populations;
- risks associated with the use of the medicine without a doctor's prescription (in relation to the active substances presented in prescription and over-the-counter forms);
- security issues related to missing information.

9.5.16.5. PSUR sub-section “Effectiveness of risk minimization measures (if applicable)”

Risk minimization measures include activities aimed at preventing side effects associated with the medicine or reducing the severity as they develop. The purpose of risk minimization measures is to reduce the likelihood of development or to

reduce the severity of side effects of medications. Risk minimization measures include routine risk minimization measures (e.g., changes in operating instructions) or additional risk minimization measures (e.g., direct notification / training of health care providers).

The sub-section should present the results of the evaluation of the effectiveness of risk minimization measures. Relevant information on the limitations and / or effectiveness of specific risk mitigation measures for significant identified risks obtained during the reporting period is presented in summary form. The evaluation results for the reporting period are presented in the appendix to the report.

#### 9.5.17. "Benefit Assessment" section of PSUR

##### 9.5.17.1. Subsection "Important Basic Information on Effectiveness in Clinical Trials and Applications in Medical Practice"

The subsection summarizes the main information on the effectiveness of the medicine in clinical trials and the effectiveness demonstrated during its application in medical practice since the beginning of the reporting period. This information must be related to the approved instructions for use.

Benefits should be characterized separately for each factor, depending on several indications, the target population, or the injectable medicine.

With respect to medicinal products where significant changes in safety profile and efficacy have been identified during the reporting period, this subsection shall contain sufficient information to substantiate the updated characteristics of the medicinal product described in Section 17.3 of the Periodically Updated Safety Report ("Benefit Characteristics"). The content and level of detail described in this section, as well as the following aspects, may vary from medicine to medicine if appropriate:

- epidemiology and source of the disease;
- characteristics of the benefit (for example, diagnostic, prophylactic, symptomatic, disease-modifying);
- Important endpoints of a clinical trial confirming the benefit (eg impact on mortality, symptoms, outcomes)
- Evidence of efficacy in medical practice and clinical trials compared to the reference medicine (eg, comparative clinical trials with active control, meta-analyses, observational studies);
- Trends and / or evidence of benefits for important population subgroups (eg, age, sex, ethnicity, disease severity, genetic polymorphism) when relevant to the benefit-risk ratio.

##### 9.5.17.2. Subsection "New information on the effectiveness of clinical trials and their application in medical practice"

New information on efficacy may be obtained from clinical trials and medical practice during the reporting period for some medicines; this information should be provided in the subsection. Separate information on the evidence base in relation to

unconfirmed instructions for use shall not be included in the section, except where it relates to the assessment of the risk-benefit ratio.

The subsection focuses on vaccines, anti-infectives, and other medicines that may affect the benefit-risk ratio over time.

The content and level of detail described in this section may vary depending on the medicine; In the absence of new information during the reporting period, reference may be made to subsection 17.1 (“Important key information on efficacy in clinical trials and medical practice”).

#### 9.5.17.3. PSUR subsection "Characteristics of benefits"

The subsection provides a combination of basic and new information on the therapeutic benefits identified during the reporting period according to the approved indications.

In the absence of new information on the benefit profile and significant changes in the safety profile, the given subsection should include a reference to subsection 17.1 (“Important key information on efficacy in clinical trials and medical practice”).

If new information on therapeutic benefits was obtained during the reporting period and there was no significant change in the safety profile, the section provides a summary of the baseline and new information combined.

In the event of significant changes in the safety profile or new data indicating that the level of therapeutic benefit is significantly lower than initially demonstrated, the section provides information on the following aspects, including a brief but critical evidence base for efficacy and safety in clinical trials and medical practice.

Evaluation should be given:

- a brief description of the level of evidence of data on therapeutic benefits; the comparative aspect of effectiveness, the degree of expression of the effect, the accuracy of statistical processing, the weak and strong aspects of the methodology, the relevance of the data in various studies / trials are considered;
- new information that, when used, casts doubt on the surrogate endpoints of clinical research;
- clinical significance of the degree of expression of the therapeutic effect; generalization of the therapeutic effect among the target subgroups (for example, information on the insufficiency of the therapeutic effect for any subgroup of the population);
- adequacy of the characteristics of the dose-therapeutic response;
- duration of the effect;
- comparative efficiency;
- to determine the level at which data on the effectiveness of clinical trials can be generalized to the population in which the medicine is used in medical practice.

9.5.18. “Integrated analysis of benefit-risk ratio according to approved guidelines” section of PSUR

The section should provide a summary assessment of the benefits and risks of the medicine during its application in medical practice by the licensee. Sub-sections 16.3 (“Risk and New Information Assessment”) and 17.3 (“Benefit Characteristics”) provide generalized information and critical analysis of the benefits and risks of the previous sections, without duplicating the information provided.

9.5.18.1. PSUR subsection "Context of benefit-risk ratio - medical needs and important alternatives to the medicine"

The sub-section provides a brief description of the medical need for the medicine according to the approved instructions and summarizes the alternatives (medicine, surgical or other alternatives; including the lack of treatment);

9.5.18.2. PSUR subsection "Evaluation of the risk-benefit ratio analysis procedure"

The benefit-risk ratio varies depending on the indications and the target populations. For this reason, the benefit-risk ratio for medicines registered under several indications should be assessed separately for each indication. If there are significant differences in the benefit-risk ratio between subgroups under the same guideline, the benefit-risk assessment should, if possible, also be presented separately for population subgroups.

a) Key issues in terms of benefits and risks:

- It should be combined to assess the key information ratios given in the previous sections on profit and risk.
- The direction of the medicine is assessed: treatment, prevention, diagnosis; severity and severity of the disease; target population (relative healthy, chronic diseases).
- In relation to the benefit, its characteristics, clinical significance, duration of the effect, generalizability, evidence of efficacy in patients who do not respond to alternative treatment, the degree of expression of the effect, the elements of individual benefit are evaluated.
- The clinical significance of the risk (eg, nature of toxicity, severity, frequency, predictability, reversibility, impact on the patient), as well as the risk aspects associated with the use of unconfirmed indications / new indications, are assessed.
- Weak and strong requirements, as well as the uncertainties of the evidence base, are considered when formulating the benefit-risk ratio assessment. A description of the limitations of the assessment performed is given.

b) A description and justification of the methodology used to assess the benefit-risk ratio is provided:

- assumptions, views, correlations confirming the result of the assessment of the benefit-risk ratio;
- comments on the possibility of expressing benefits and risks in a presented way and their mutual comparison;

- if a quantitative assessment of the ratio is provided, a generalized description of the assessment methods shall be included;
- economic valuation (eg cost-effectiveness) should not be taken into account when assessing the benefit-risk ratio.

#### 9.5.19. "Results and measures" section of PSUR

The final section of the PSUR should include a conclusion on the overall assessment of the benefit-risk ratio for each approved indication of all new information discovered during the reporting period, as well as, where appropriate, on patient subgroups.

Based on a cumulative assessment of safety data and an analysis of the benefit-risk ratio, the licensee should assess the need for changes to the medicine information and suggest the context of the relevant changes.

The result should include initial proposals for further assessment or optimization of the benefit-risk ratio for further discussion with the relevant body. These proposals may include risk minimization measures.

Proposals for medicines with a pharmacovigilance plan and a risk minimization plan should be included in the pharmacovigilance plan and risk mitigation plan.

#### 9.5.20. "Add to PSUR" section of PSUR

PSUR must contain the following supplements:

1. Reference information
2. Cumulative summary table information on serious adverse events detected during clinical trials / trials; and cumulative and interval aggregate table data on serious and non-serious side effects on post-registration usage data
3. Schedule information on signals (if not included in the main part of PSUR)
4. List of all post-registration safety surveys (List of all post-registration interventional and non-interventional safety surveys funded by the licensee whose purpose is to identify, characterize and quantify safety problems, or to validate the safety profile of a medicinal product or to assess the effectiveness of risk mitigation measures).
5. List of data sources used in the preparation of PSUR
6. Proposed projects on information related to the medicine (instructions for use and brief description of the medicine)
7. Proposed additional pharmacovigilance measures and risk minimization measures
8. Generalized information on medicine safety issues at the beginning of the reporting period in accordance with the wording of module SVII of Part II of the risk management plan
9. Final reports of all post-registration safety surveys (All post-registration funded by the licensee whose purpose is to identify, characterize and quantify safety problems, or to approve the safety profile of a medicinal product or to assess the effectiveness of risk mitigation measures or risk mitigation measures) final reports of interventional and non-interventional security studies)

10. Reports on the results of research or other measures to assess the effectiveness of risk mitigation measures.

#### 9.6. Quality system of PSUR at the level of the license holder

The holder of the license must have the structures and processes established for the control over the preparation, quality control, inspection and submission of PSUR, as well as during the process and after their evaluation. These structures and processes should be described in the written procedures of the licensee's quality system.

Pharmacovigilance processes include a number of areas that may directly affect the quality of PSUR (eg, spontaneous notification or processing of notices of side effects obtained in clinical trials; literature review; signal detection, validation and evaluation; pharmacovigilance and post-registration research activities). additional measures; procedures for data processing and aggregation in risk and benefit assessment, etc.). The quality system should describe the interrelationships between all relevant information collection procedures, commitments, processes and information channels for inclusion in the PSUR. Documented process quality control procedures should be developed and applied to ensure the completeness and accuracy of the information provided in the PSUR. The importance of an integrated risk-benefit assessment determines the need to ensure the contribution of different departments / divisions in the development of the PSUR.

It should include an assessment of the Institution's special inquiries on aspects of the PSUR's security profile. The holder of the card must have a mechanism to ensure that the requests of the Institution are properly processed and responded to.

In order to ensure the accuracy and completeness of the information provided on additional impacts / adverse events, the submission of aggregated table data should be subject to the procedure of verification of data in relation to the licensee's databases. The placement of queries in the database, the parameters used to extract the data and the quality control must be reliably documented.

The license holder's Good quality system must exclude the risk of non-compliance by the license holder with the requirements of the legislation in accordance with the following:

- non-submission of the report: incomplete submission of PSUR, violation of the schedule or timing of PSUR transmission (without the prior consent of the Institution);
- unreasonable failure to provide the requested information;
- low quality of reports (insufficient documentation or insufficient information or assessment of new security information, safety signals, risk assessment, integrated assessment of benefit assessment and risk-benefit ratio, lack of instructions on misuse, lack of standard terminology , unreasonable exclusion of cases, failure to provide information on risk factors);
- Submission of PSUR without reflecting previous inquiries received from the Institution.

Any deviations from the PSUR preparation and submission procedure should be documented and appropriate corrective and preventive measures taken. This document must be available at any time.

In case of transfer of the executive authority for the preparation of PSUR to third parties, the licensee must ensure the existence of a Good quality system in the relevant third party that meets the requirements of the legislation.

### **9.7. Staff training on PSUR procedures**

It is the responsibility of the person in charge of pharmacovigilance to ensure that the pharmacovigilance personnel involved in the preparation, review, quality control, evaluation and submission procedures of the PSUR are trained, qualified and experienced in the evaluation and quality control of medical information. If necessary, necessary training is provided on various components of the process, knowledge aspects and skills. Areas of training should include legislation, guidance from management, scientific evaluation of data, and written procedures on aspects of PSUR preparation. Documentation of the training process should confirm that the training was conducted prior to the implementation of the relevant functions of the STS.

### **9.8. Procedure for submission of PSUR**

#### **9.8.1. Standard presentation procedure of PSUR**

The timing and frequency of PSUR of medicines is available on the official website of the European Medicine Agency at the link "List of EURDs and frequency of submission of PSURs" on the official website of the European Medicines Agency. is determined based on the list.

For medicines that are not included in the list of international non-patented names, the frequency of submission of PSUR is as follows:

- for the first 2 years after the state registration of the medicine in the Republic of Azerbaijan or every 6 months from the date of international birth;
- once a year for the next 2 years;
- subsequently - every 3 years.

The period for submission of PSUR information from the date of lock shall not exceed 90 calendar days.

#### **9.8.2. Extraordinary issuance of PSUR**

Upon receipt of a written request from the institution, the PSUR must be sent no later than 60 calendar days from the date of receipt of the request.

#### **9.8.3. Form of submission of PSUR**

PSUR is submitted to the Institution together with the official cover letter.

### **9.9. PSUR assessment process**

In order to determine compliance with the requirements of the legislation, as well as possible changes in the safety profile of the medicine and the impact of these

changes on the assessment of the benefit-risk ratio of the medicine, the Agency should ensure the assessment of STDs. As a result of the assessment, an expert opinion is prepared.

## **10. Signal management process**

### 10.1. Structures and processes

#### 10.1.1. Sources of signal reception and their processing

10.1.1.1. Sources of signal reception include all information obtained during the application of the medicine, including pre-clinical, clinical data, pharmacovigilance methods and quality control systems. The data may include details obtained through spontaneous notification systems, active monitoring systems, non-intervention studies, clinical trials, and other information sources.

10.1.1.2. Signals from spontaneous notifications may be included in the Additional Impact Notice (SID) entered into the Side Impact Database, in scientific literature articles, in periodically updated safety reports, or as part of regulatory procedures (eg post-registration research commitments, changes, additions, and revisions). registration) or other information provided by licensees as part of ongoing monitoring of the benefit-risk ratio of the medicinal product.

10.1.1.3. Signals can be detected during various types of research / testing, including pre-clinical, interventional and non-interventional studies, systematic reviews, and meta-analyzes. Active monitoring can help detect different types of signals, as well as stimulate the process of reporting specific types of side effects by professionals.

10.1.1.4. Other sources of information include Internet resources, digital media (such as publicly accessible websites, social networks, blogs), or other systems that allow patients and consumers to report notifications of side effects.

#### 10.1.2. Methodology of signal processing

10.1.2.1. When detecting signals, a structured and accepted methodology should be followed, which can vary depending on the type of medicine for which the procedure is performed.

10.1.2.2. A structured and accepted methodology should be used to assess the evidence base that confirms the incoming signal; this methodology should take into account the clinical significance, the degree of reliability of the interaction, the relevance of the data, the correlation of the reaction and the degree of impact, the cause-and-effect relationship, the relevance of biological reality, experimental results, and possible similar information.

10.1.2.3. Various factors are taken into account when determining the priority of signals: factors such as whether the detected interaction or medicine is new, the importance of the interaction, the severity of the relevant effect, and the documentation of the notification.

#### 10.1.3. Signal processing process

##### 10.1.3.1. Introduction

10.1.3.1.1. The signal processing process includes all stages from signal detection to the development of recommendations. The signal processing rules apply to all stakeholders involved in monitoring the safety of registered medicines.

10.1.3.1.2. The signal processing process consists of the following stages:

- signal detection;
- signal validation;
- signal analysis and prioritization;
- signal evaluation;
- recommendations on activities;
- information exchange.

10.1.3.1.3. Although these steps typically expect a logical sequence, the wide range of available information sources used to detect signals may require flexibility in signal processing. For example:

- a) When signal detection is based primarily on ICSRs, the procedure may include verification and initial prioritization of the detected signal.
- b) As a rule, it is not possible to assess each ICSR if the signal is detected based on the generalized results of the study, and additional data may be required as a result of validation.
- c) Action recommendations and information sharing are components that need to be considered at each stage of the process.

10.1.3.2. Alarm detection

10.1.3.2.1. The following requirements apply to all signal detection methods:

- the method used should be appropriate to the amount of data; for example, the use of complex statistical methods may not be appropriate for small volumes of data;
- information from all relevant sources should be taken into account;
- there should be systems to guarantee the quality of data discovery activities;
- the results of the summary review of the cumulative data should be evaluated in a timely and Good manner by an authorized specialist;
- immediate and effective action must be taken when a threat to public health is identified;
- the process of signal detection, including the justification of the frequency of detection activities and the method of detection, must be reliably documented.

10.1.3.2.2. The detection of security signals can be based on a review of the FHD database, statistical analysis of large databases, or a combined approach based on a combination of the two methods.

10.1.3.2.3. Review of ICSRs

ICSRs can be obtained from spontaneous notification systems, active monitoring forms, clinical trials, or published in the medical literature. Even a notification of a serious or severe side effect (for example, a notification of anaphylactic shock) is sufficient to draw attention to this notification and to take further action. The number of informational assessments to be evaluated (after removal of recurring

notices and invalid notifications), patient demographics (eg, age and sex), suspected medication (eg, injected dose), and side effects (eg, signs and symptoms), temporary interactions the relationship, the clinical outcome of discontinuation of the medicine, the existence of potential alternative causes of adverse events, the assessment of the cause-and-effect relationship by the sender, as well as the validity of the biological and pharmacological relationship.

#### 10.1.3.2.4. Statistical analysis in large databases

There are various statistical methods for automatic detection of signals based on the disproportionate number of reports (i.e., the higher notification level of suspected side effects against the relevant active substance / medicine compared to other active substances / medicines in the database). The use of statistical methods is not suitable for all cases. The use of statistical methods and the selection of signal identification criteria should take into account the amount of data, the completeness of the available information and the severity of the additional impact.

The frequency of statistical analysis of the database and the preparation of the statistical report depends on the characteristics of the active substance / medicine, the instructions for use, as well as potential and identified risks.

#### 10.1.3.2.5. A combination of statistical methods and a review of ICSR

Statistical reports may be intended to detect suspicious side effects that meet the estimated criteria of frequency, severity, clinical significance, novelty, or statistical correlation. Such filtering methods may facilitate the selection of more important ICSRs considered in the first stage of the procedure. The limit value of the indicator used in this filtration process (for example, not less than 3 notifications) may vary depending on the clinical significance of the suspected side effect and signal, the impact on public health, and the prevalence of medicine use.

When using automatic screening in the signal detection process, the relevant ICSRs should be studied separately in the future.

Regardless of the statistical method used, the signal detection procedure should always include a clinical evaluation. The statistical method is an additional method of signal detection and validation.

#### 10.1.3.3. Signal validation

10.1.3.3.1. Once the signal is detected, the data is evaluated to verify and confirm that the existing information contains sufficient evidence to identify a new potential cause-and-effect relationship or a new aspect of a previously established interaction. Validation results determine the need for further evaluation of the signal.

Regardless of the source of the signal, the following must be taken into account when performing the signal validation procedure:

a) Clinical significance, for example:

- level of evidence base for confirmation of cause-and-effect relationship (eg number of notifications taking into account effect, transient interaction, validity /

probability of side effect development mechanism, results of medicine rejection and re-administration, alternative explanation / other causal factors);

- severity of side effects and their consequences;
- impact-related innovation (eg, new and serious side effects);
- clinical context (for example, suspicion of clinical syndrome, including other reactions);
- Possible medicine interactions and reactions in specific patient groups.

b) Previous information:

- the information is already included in the instructions for use or brief description of the medicine;
- the signal has already been evaluated by the Agency in the PSUR or RIP, or discussed at the level of a scientific expert committee, or formed the basis for a regulatory procedure.

As a rule, signals not mentioned above are validated. However, validation of known signals in case of doubt in terms of frequency of development, duration, severity or outcome (eg, lethal outcome found in the interaction) compared to the data / characteristics previously included in the operating instructions or reviewed by the Agency may be required.

c) Availability of other relevant sources of information with a large amount of information on a specific additional impact:

- literature information on relevant notifications;
- experimental or pre-clinical results;
- Review of larger databases.

10.1.3.3.2. If the verification process of all relevant documentation indicates a probable new cause-and-effect relationship or a new aspect of a known interaction and thus constitutes a justification for a subsequent assessment, the signal acquires the status of a validated signal.

10.1.3.3.3. In the validation process, a new cause-and-effect relationship or a new aspect of an existing interaction may require further analysis for an unconfirmed signal (for example, if there is a lack of documentation on the relevant additional impact event). Where appropriate, notices of new impacts or subsequent observations on previous events from the post-registration observation period should be reviewed at appropriate intervals to ensure that all relevant notices are accounted for and reviewed.

10.1.3.3.4. Licensees and the Authority shall take into account the validation results of the signals, including the reasons why the signals were not perceived as evidence of a probable new cause-and-effect relationship or a new aspect of the existing interaction, and to study and track information that may assist must have tracking systems.

10.1.3.4. Analysis and prioritization of signals

10.1.3.4.1. A key element of the signal management process is the immediate determination of their effect on public health or the benefit-risk ratio of the

medicine in affected patients. The following should be considered during the assessment:

- severity, consequences, reversibility and prevention potential of additional effects;
- assessment of the impact and frequency of side effects on the patient;
- impact on public health, depending on the degree of use of the medicine in the general patient group and vulnerable population groups and / or other methods of medicine use (eg, misuse or over-the-counter use);
- the consequences of discontinuation of treatment due to the course of the disease and the availability of other therapeutic alternatives;
- the degree of probable impact on the planned regulatory measures (for example, the addition of additional effects, precautions, contraindications, the application of additional risk minimization measures, discontinuation of use, recall from sale);
- the possibility of applying the signal to other active substances belonging to a similar pharmacotherapeutic group.

10.1.3.4.2. In some cases, special attention should be given to signals in the media that are highly publicized or important to public health (for example, adverse reactions to immunization) in order to bring the results of the assessment to the attention of health professionals and the public.

10.1.3.4.3. The outcome of the signal prioritization procedure should include a recommendation on the time frame for signal evaluation.

10.1.3.4.4. The result of the signal priority procedure should be entered into the tracking system, indicating the justification for the established priority level of the signal.

10.1.3.5. Evaluation of signals

10.1.3.5.1. The purpose of signal evaluation is to quantify the interaction (preferably in absolute terms) and to study the evidence of a cause-and-effect relationship between the suspected medicine and the side effect in order to determine the need for additional data collection or regulatory action. The assessment consists of a detailed pharmacological, medical and epidemiological study of all available information on the relevant signal. The review should contain available pharmacological, pre-clinical and clinical information and be as complete as possible in relation to the sources of information (including medicine dossier information and subsequent changes at the time of application, literature articles, spontaneous notifications, and unpublished information of licensees). . The recommendations of foreign experts should also be taken into account. If information is obtained from multiple sources, their level of evidence and limitations should be taken into account in order to assess their contribution to the assessment of the security issue. Aggregate information from a variety of sources also requires a choice of internationally accepted terminology for medical events. In the absence of such a terminological definition, an employee definition is necessary.

10.1.3.5.2. In some cases, signals should be evaluated according to the organ class or therapeutic level of the system, or at the level of a standardized query in the MedDRA dictionary of medical terms.

Search for information, for example, on other terms related to complex diseases (eg, optic neuritis - as the first possible sign of multiple sclerosis), early stage of the reaction (eg, prolongation of the QT interval) or clinical complications of relevant side effects (eg, dehydration or acute renal failure). deficiency) may require the inclusion of other medicines and other side effects within the same class.

10.1.3.5.3. Gathering information from a variety of sources can take time. In order to optimize the process, for example, the method of stepwise signal evaluation can be used. As a result of the first phase of the assessment, there may be a potential risk that needs to be eliminated based on the available information, and temporary measures may be taken in response to the new signal of a severe adverse reaction.

10.1.3.6. Recommendations on the activities of the institution

10.1.3.6.1. Recommendations on the results of the assessment may vary in accordance with applicable law and the decision on the results of the assessment of the signal.

As a rule, recommendations are made based on aggregate information after signal evaluation, however, the need for activities is assessed throughout the signal management process by justifying and determining the appropriateness of earlier risk mitigation activities.

10.1.3.6.2. If suspicious side effects develop mechanisms suggest the possibility of preventing or reducing the severity of the side effects, the results of the signal assessment may include activities, additional research, or risk minimization measures. If the result is based on limited information, post-registration security research may be required to investigate the security problem / potential issue.

10.1.3.6.3. If the institution requires the licensee to carry out additional activities, such a request must indicate when the activities (including reports on successful outcomes and interim outcomes in proportion to the impact of the security problem on public health and severity) must be completed. The Licensee and the Authority shall take into account the parameters of the security issue under investigation, for example, the need for a prospective design of the study and the frequency of development, and the possibility of conducting the study at the appointed time. Temporary measures to safely and effectively use the medicine or to eliminate the risks, including the possibility of suspension of the medicine registration card, should be considered.

10.1.3.6.4. Where there is no risk to patients, the Authority may decide that there is no need for further assessment or follow-up.

10.1.3.7. Information exchange

10.1.3.7.1. It should be possible to exchange information between the Authority, licensees and other parties in order to disseminate information about the signals,

collect additional information, further assess the safety issue and make a decision on the protection of patients' health. Temporary information exchange requirements may vary depending on the security issue, but information about signals should be disseminated immediately after their validation procedure has been completed and the signal is considered valid.

10.1.3.7.2. Licensees provide all relevant information about the signal to the Institution (as part of their commitment to monitoring the benefit-risk ratio of the medicine and pharmacovigilance). Validated signals that may affect public health and the benefit-risk ratio of the medicinal product should be communicated to the Institution immediately, as well as suggestions for possible action, if appropriate.

10.1.3.7.3. The agency transmits the results of the evaluation of the signals to the licensees.

#### 10.1.4. Quality requirements

##### 10.1.4.1. Follow-up

Validation, prioritization, evaluation, deadlines, decisions, activities, plans, notifications, as well as other key procedures should be reliably documented and monitored periodically. Tracking systems should also be documented and include signals that, based on the results of the test, result in the absence of a new potential cause-and-effect relationship or a new aspect of a known interaction, so that they can receive special attention in subsequent analysis. All records should be archived and stored in accordance with applicable procedures.

##### 10.1.4.2. Quality systems and documentation

10.1.4.2.1. An important feature of the signal processing system is to ensure Good and efficient operation of the system, standardization of obligations and required activities, implementation of these activities by qualified persons and their comprehensibility for all parties involved, Good control and improvement of the system if necessary. is an accurate documentation. Based on the requirements, a quality assurance and control system should be developed in accordance with the quality system standards that should be applied to all signal management processes. Detailed quality system procedures should be developed, documented and applied. Roles and responsibilities should be assigned to the company's activities and documentation, quality control and quality studies, as well as corrective and preventive measures. It should also include obligations for the audit of quality assurance in the signal management system, as well as for the audit of subcontractors of the parties to the contract who perform any work in this direction. The confidentiality, security and reliability of information and documentation (including completeness at the time of transmission) must be guaranteed.

10.1.4.2.2. The tracking system should ensure that information on the results of the audit is obtained by each of the parties involved, indicating the signal processing activities, relevant inquiries and their results. The information obtained, searches, search results, evaluations and decisions on potential signals (positive and

negative), as well as the results of signal verification should be archived. The data must contain the validation results of the signal.

10.1.4.2.3. An examination of the certificate holder's documentation of compliance with these provisions prior to and after the registration procedure may be required to assess the activity or inspection performed.

#### 10.1.4.3. Training

Personnel must be specially trained to perform signal processing activities in accordance with assigned functions and responsibilities. This process may include not only the staff of the pharmacovigilance department, but also the staff of the legal department, pre-clinic, medical, pharmacoepidemiological and marketing research staff who can receive information about potential signals or participate in the signal processing process. Training should include terminology and existing databases with signal sources. The procedures of the training system and the placement of information on the training should be reliably documented, the work experience of the specialists and the description of the functions performed should be archived.

## **10.2. Roles and responsibilities**

### 10.2.1. Role and responsibilities of the organization

Institution:

- manages information in its territory, including information obtained from other sources specified in subsection 10.1.1;
- performs validation of signals received from accessible sources and other stages of the processing procedure;
- Submits signals that have undergone validation and evaluation procedures to the relevant expert committee for further study or to determine the feasibility of further risk mitigation activities.

### 10.2.2. Role and responsibilities of the card holder

license holder:

- manages all available data and information on signals;
- manages all information obtained in databases and performs international detection of signals; detection of signals shall include their validation, taking into account the components of the information provided in sub-clause 10.1.3.3;
- validates all detected signals and informs the Agency about them;
- informs the Agency in case of detection of emergency security problems during the implementation of signal detection activities;
- cooperates with the Agency in the implementation of signal evaluation procedures by providing additional information on the request;
- ensures that all signal detection procedures can be audited.

### 10.2.3. Subsequent regulatory processes

In the event that the Institution decides on the need for additional activities, the signal shall be assessed in a timely manner in accordance with the degree and

severity of the security problem, and further activities shall be agreed upon in accordance with the registration card. Based on the results of the procedure, the following decisions can be made:

- no additional assessment or action is required;
- the certificate holder must carry out additional assessment of the data and submit the results of such assessment at the appointed time;
- the licensee must submit the PSUR, taking into account the newly discovered aspect of the security profile;
- the license holder must finance the post-registration survey in accordance with the approved protocol and present the final results of such research;
- the licensee must submit the RMP or its updated version;
- the licensee must take the necessary measures to ensure the safe and effective use of the medicine;
- registration status is changed: registration should be suspended, canceled or not re-registered;
- urgent security restrictions should be applied;
- unscheduled inspection of the pharmacovigilance system should be carried out in order to confirm that the license holder complies with the requirements of the legislation on the pharmacovigilance system;
- the suspected medicine must be included in the list of medicines under special control.

#### 10.2.4. Transparency

The competent authorities should monitor the timeliness of the dissemination of important information on security issues identified by the pharmacovigilance system to the public by publishing it on a web portal or by other available means of communication.

## **11. Post-registration security surveys**

### **11.1. Introduction**

Post-registration safety examination of a medicinal product may be carried out voluntarily by the licensee or in accordance with the obligation of the Institution on the condition of issuance of the registration certificate, or by conducting research related to the registered medicinal product. It can then be initiated, controlled or funded.

Post-registration safety research can be clinical research / testing or non-intervention research / testing.

### **11.2. Structures and processes**

#### 11.2.1. Areas of application

The requirements of this section apply to unregistered post-registration security surveys initiated, monitored or funded by the licensee in the country, either voluntarily or in accordance with the obligations of the Authority. Post-registration

safety surveys include surveys that collect information from patients and health care providers, as well as studies that reuse information previously obtained for other purposes and stored in patients' medical records or other forms of data storage (as well as electronically).

If post-registration safety research consists of clinical trials, sub-clause 16.3 of the Regulation shall be observed during its implementation.

### **11.3. Terminology**

**Research start date** - start date of data collection.

**Initiation of data collection** - registration date in the form (database) of data collection on research / test data on the first patient included in the study / test, or in case of re-use of data - date of data extraction.

**End of data collection** - the date on which the analytical database is first fully accessible.

### **11.4. General principles**

The primary purpose of post-intervention safety research should be to obtain scientific information that is important or potentially clinically relevant to public health. Such research should not be done if it helps the medicine to advance in the market.

The objectives of post-registration security research may include:

- quantitative assessment of potential or identified risks, for example, assessment of the frequency of occurrence of relative risks in a population that does not accept a given medicine or in a population that receives another medicine or class of medicine; as well as the study of risk factors and factors that alter the effect of the medicine;
- risk assessment of the medicine used according to the approved indications in the groups of patients who were not studied or insufficiently studied at the pre-registration stage (for example, pregnant women, special age groups, patients with renal or hepatic insufficiency);
- risk assessment of long-term use of the medicine;
- confirmation that there are no risks of medicines;
- evaluation of standard clinical practice of the medicine, obtaining additional information on the safety of the medicinal product (eg, instructions for use, dosage, concomitant treatment, medical errors);
- Evaluate the effectiveness of risk minimization measures (eg, study of medicine use aspects, survey of patients or healthcare professionals).

When developing research protocols, conducting research and compiling research reports, appropriate scientific guidance should be taken into account by the license holders. In order to evaluate research protocols and research reports, the Agency should also take into account the existing scientific guidelines and methodological standards in pharmacoepidemiology.

Regarding post-registration security research sponsored and licensed by the licensee and fully or partially developed, conducted and analyzed by the licensee, the licensee must ensure that the researchers have the necessary qualifications in education, training and practice to perform their duties. .

### **11.5. Research protocol**

All post-registration safety research should be conducted in accordance with a scientifically based research protocol developed by persons with appropriate scientific training and experience.

Regarding voluntary post-registration safety surveys, it is recommended that the license holder submit the survey protocol to the Institution where the unregistered post-registration safety surveys of the medicinal product are planned to be conducted prior to the start of data collection.

In accordance with the obligation of the Authority to conduct post-registration security surveys initiated by the Licensee, the Licensee shall ensure that research information, including the research plan, is submitted to the Authority for post-registration security research prior to the start of data collection. If post-registration security surveys are conducted simultaneously in the territories of other States, the relevant authorities shall be notified by providing a brief description of the survey protocol.

In order to fulfill the obligations of the card holder to carry out pharmacovigilance activities, the person responsible for pharmacovigilance must be involved in the procedure for reviewing and approving research protocols. The Pharmacovigilance Coordinator must be informed at the national level of any post-registration security research, as well as obtain a copy of the research protocol.

#### **11.5.1. Format and content of the research protocol**

The research protocol should be in the following format:

11.5.1.1. Name of post-registration safety study: an informative name containing the general terminology that defines the design of the study and the medicine or group of medicines being studied, as well as a subheading indicating the date of editing and the last edition.

11.5.1.2. License holder: name and address of the license holder.

11.5.1.3. Responsible parties: names, positions, qualifications, addresses and information on all responsible parties, including the first author of the protocol, chief researchers, research coordinators of each country and research centers where the research was conducted. A list of all institutions and researchers involved in the study should be available upon request of the Institution.

11.5.1.4. Brief description: A separate summary of the research protocol, which includes the following subsections:

- the name of the research with subheadings, including the version of the editorial board and the history of the protocol, as well as the name of the first author of the protocol and information about the main place of work;

- substantiation and preliminary conditions of conduct;
- goals and objectives of the research;
- research design;
- studied population;
- monitored indicators;
- sources of information;
- size of the study (sample size);
- data analysis;
- main stages.

11.5.1.5. Changes and updates: Any significant changes and updates made to the protocol after the start of data collection, including the justification for each change or update, the date of each change, and a reference to the modified section of the protocol.

11.5.1.6. Main stages: information in tabular form with indication of planned dates for the implementation of the following main stages of the research:

- start data collection;
- completion of data collection;
- report on the progress of the research (s);
- Interim report on research results (s), if applicable;
- final report on research results.

Information on any other important stages of the research should be provided.

11.5.1.7. Prerequisites and Prerequisites: A description of the risk management measures, security problem, and security profile that led to the study, as well as an assessment or retrieval of relevant safety information. critical analysis of data. This analysis may include the results of relevant experiments on animals, clinical studies, statistical population data, and data from previous epidemiological studies. It should also include references to the results of similar studies and the expected contribution of the given study.

11.5.1.8. Objectives and goals of the research: the purpose of the research, including the purpose of the research, explaining how it will contribute to solving the problem that caused it, as well as any initial assumptions and key theses describing the data or information to be obtained as a result of the research.

11.5.1.9. Research methods: description of research methods, including:

11.5.1.9.1. Research design: a description of the research design and a rationale for the appropriate choice.

11.5.1.9.2. Conditions: research population defined by selection criteria, periods, places, and categories of individuals. An objective justification of all inclusion and exclusion criteria and a description of their impact on the number of research subjects available for further analysis is essential. If any selection is made for the target population, a description of the target population and details of selection methods should be available. If the design of the study is a systematic review or

meta-analysis, it is necessary to explain the selection criteria and the suitability of the research.

11.5.1.9.3. Variables: outcome, effects, and other variables, including measurable risk factors, potential factors, distorting outcomes, and impact variables, including job definitions.

11.5.1.9.4. Sources of data: data sources and strategies for identifying effects, outcomes, and other variables for research purposes, such as potential factors, misleading results, and impact variables. If validated data sources, tools, and measurements are used, a description of the validation method is necessary. If methods of obtaining data or tools are tested in pilot studies, it is necessary to provide a pilot research plan. It is necessary to provide a description of all participating expert committees and evaluation procedures that will be used to validate the diagnoses. If the study uses existing data sources such as electronic medical records, it is important to provide all the information regarding the reliability of the records and data coding. In the case of a systematic review or meta-analysis, it is necessary to have a description of the strategy and search processes, as well as any methods to validate the researchers' data.

11.5.1.9.5. Size of the study (sample size): the planned sample size, the planned accuracy of the research results, and the calculation of the sample size that can minimize the initially determined risk with the initially determined force.

11.5.1.9.6. Data management: statistical software and data management to be used in the research process. Procedures for data collection, recovery and preparation.

11.5.1.9.7. Data analysis: all the important steps from raw data to the final result, including the methods used to correct inconsistencies or errors, incorrect values, to modify raw data, to categorize, analyze and present the results, as well as the sources of errors and procedures for verifying their impact on results; any statistical procedures applied to the data to obtain Good intervals and point-to-point estimates of any sensitivity analysis and correlation or frequency measurements.

11.5.1.9.8. Quality control: a description of the mechanisms and procedures to ensure the quality and completeness of the data, including the accuracy and readability of the data obtained and the original documentation, the storage of records and the archiving of statistical programs; description of available information on record verification and validation of endpoint validation procedures. Where appropriate, information on the certification and / or qualification of any ancillary laboratory or research team shall be included.

11.5.1.9.9. Limitations of research methods: Any potential limitations of research design, data sources, and analytical methods, including errors, generalizations, random errors, and problems with distortion of results. The probability of success of measures aimed at reducing the number of errors should be discussed.

11.5.1.10. Protection of research subjects: security measures to ensure compliance with national requirements for the welfare and rights of participants in post-registration security research without interference.

11.5.1.11. Adverse event / side effect information management and reporting: Procedures for the collection, management and presentation of any new information that may affect the benefit-risk assessment of ICSRs and medicines during research.

11.5.1.12. Plans for dissemination of information obtained and communication of research results, including plans for submission of current reports, final reports and publications.

11.5.1.13. References.

The section may contain any additional or ancillary information on specific aspects that has not been previously considered (eg, questionnaires, notification forms). Surveys to assess the feasibility of the protocol, such as testing questionnaires / questionnaires to determine the statistical accuracy of the survey or simple calculations of medical events or appointments in the database, should be included in the relevant section of the study protocol with a brief description of methods and results. . Performance assessments that are part of the research process should be fully described in the protocol (for example, a pilot assessment of a questionnaire used for patients).

11.5.2. Monitoring of changes in the research protocol

Changes and updates to the research protocol should be made as necessary in the course of the research. Any significant changes made to the protocol after the start of the study should be recorded in such a way that these changes, as well as the date of the changes, can be tracked and verified. If changes to the protocol result in the study being accepted as a post-registration uninterrupted study / trial, the study shall be conducted in accordance with applicable law in accordance with the requirements of applicable law on the organization and conduct of clinical trials / trials.

Regarding voluntary post-registration security surveys, it is recommended that the license holder submit the survey protocol, along with any changes / updates, to the competent authority in the area where the post-registration uninterrupted security survey is conducted.

With regard to post-registration security surveys initiated by the licensee in accordance with the institution's obligation, the licensee must ensure that information on the inclusion of any significant changes in the research protocol is provided to the competent authority before such changes are applied.

## **11.6. Submission of pharmacovigilance information to the Agency**

11.6.1. Important information for assessing the benefit-risk ratio of the medicine  
The holder of the license checks the information obtained during the research and evaluates their effect on the benefit-risk ratio of the relevant medicine. Any new

information that may affect the assessment of the benefit-risk ratio of the medicinal product shall be immediately reported to the competent authorities, which was conducted in the area of post-registration safety research and registered in the area of the medicinal product under study. Information that may affect the assessment of the benefit-risk ratio of a medicinal product may include information obtained from the analysis of notifications of suspected adverse effects or the results of an interim analysis of aggregated safety data.

Where appropriate, this information should not affect the information on the research findings provided in the PSUR and in the RMP updates.

11.6.2. Suspicious side effects and other safety information that needs to be reported immediately

Information on unforeseen serious adverse effects and other safety information shall be provided to the Agency as a matter of urgency in accordance with sub-clause 16.3 of the Rules.

Collection of data on side effects, data management (including, if appropriate, review and evaluation by the licensee) and submission of notices of suspected side effects should be carried out in clinical research centers and should be summarized in the research protocol.

11.6.3. Research reports

11.6.3.1. Interim report

The organization may require the submission of an interim report on post-registration safety surveys carried out in respect of medicines registered in the territory of the Republic of Azerbaijan. Requests for the submission of interim reports may be made at any time prior to the start of the study or during the course of the study. The reason for the request may be information related to the safety or efficacy profile that emerged during the study, or the need to obtain information on the progress of the study in the context of regulatory procedures, as well as important information on the safety of the medicine.

The timing of the submission of interim reports should be agreed with the relevant body and specified in the research protocol. The progress of post-registration security surveys should, where appropriate, be reflected in the PSUR and RMP updates as appropriate.

Logical consistency should be expected in the content of the interim report and all available information relevant to the course of the study, such as the number of patients included in the study, the number of patients exposed to the medicine or difficulties in conducting the study, deviations from the plan and monitoring results. must contain information. Additional information may be required by the Institution after reviewing the report.

11.6.3.2. Final report of the research

The final report of the post-registration security survey shall be submitted to the Institution as soon as possible, but not later than 12 months from the date of the lock.

It is recommended that the final report on the study, as well as post-registration safety surveys initiated voluntarily by the holder, be submitted to the competent authorities of the States where the medicinal product is registered.

If the licensee is not allowed to deviate from the requirements for post-registration security surveys initiated by the licensee in accordance with its obligation, the agency must submit a final report on the survey, including a summary of the study, for publication within 12 months of data collection.

In case of termination of the study, a final report and an explanation of the reason for the termination of the study shall be provided.

The final report of the post-registration security survey should include the following sections and information:

11.6.3.2.1. Title: a title containing general terminology indicating the design of the study; subheadings indicating the date of the final report, the name of the main author of the report and details about it.

11.6.3.2.2. Summary: A separate summary in the format presented below

11.6.3.2.3. License holder: name and address of the license holder.

11.6.3.2.4. Researchers: names, titles, academic degrees, addresses and details of all researchers, as well as a list of all organizations and research sites involved in the research.

11.6.3.2.5. Stages: planned and actual dates of the following stages of the study:

- start data collection;
- completion of data collection;
- Report on the progress of the research required by the institution;
- Interim report on research results, if appropriate;
- final report on research results;
- any other important stages applied to the research, including, if applicable, the date of approval of the protocol by the ethics commission and the date of registration of the research in the electronic register of research.

11.6.3.2.6. Prerequisites and Prerequisites: A description of the security problem that led to the study, as well as a critical analysis of all published and unpublished available information, including an assessment of the security or lack of relevant knowledge, which constitutes the direction of the research.

11.6.3.2.7. Research goals and objectives: The research goals and objectives, including any initial assumptions as indicated in the test protocol.

11.6.3.2.8. Changes and updates: A list of any significant changes and updates made to the initial test protocol after the start of data collection, including a justification for each change or update.

11.6.3.2.9. Research methods:

- Research design: key elements of research design and justification of the selected design.
- Conditions: terms, locations and relevant dates of the study, including patient collection periods, follow-up follow-up periods and data collection periods. In the

case of a systematic review or meta-analysis - along with the characteristics and justifications of the research used as acceptance criteria.

- Patients: any target population and criteria for inclusion of patients in the study. Sources and methods of selection of participants, including methods of individualization of cases, if appropriate, as well as the number and reasons of exclusion from the study.
- Variables: operational definitions, including all outcomes, effects, prognostic factors, potentially distorting factors, and impact variables. Where appropriate, diagnostic criteria are provided.
- Data sources and measurement: for each variable under consideration, data sources, a detailed description of the methods of estimation and measurement (if applicable), as well as the comparability of estimation methods if there are more than one. Where available sources of information, such as electronic medical records, are used in the study, it is important to disclose any information regarding the reliability of the coding of records and data. In the case of a systematic review or meta-analysis, all data sources, search strategies, research selection methods, data extraction methods, and all processes for obtaining and validating researchers' data should be described.
- Errors: a description of actions / measures taken to deal with potential sources of error.
- Size of the survey (sample size): justification of the sample size, the calculation used for the sample size and the method of obtaining the intended sample size.
- Data transformation: transformations, calculations or data operations, including methods of processing quantitative data during analysis, justification of selected methods for data grouping.
- Statistical methods: description on the following aspects:
  - basic methods of generalization;
  - all statistical methods used in the research, including methods of checking distortions and methods of combining research results in relation to meta-analyses;
  - any methods used to study subgroups and interactions;
  - approach to solving problems on inaccessible information;
  - assessment of research sensitivity;
  - all changes in the data analysis plan provided for in the research protocol, together with the justification of these changes;
- Quality control: mechanisms and procedures to ensure data quality and completeness.

11.6.3.2.10 Results: Provide tables, graphs and illustrations to reflect the data obtained and the analysis performed. Both adjusted and non-adjusted results must be presented. Evaluation of data accuracy should be done quantitatively, indicating reliability intervals. This section should include the following subsections:

- participants: the number of participants in each phase of the study (for example, the number of potentially relevant, screened, validated, included in the study,

completed follow-up and analyzed, as well as the reasons for exclusion at any stage). In the case of a systematic review or meta-analysis, the number of those screened, assessed for compliance, and included in the review of the study, indicating the reasons for exclusion at each stage.

- descriptive information: information on the characteristics of the research participants, the impact and potential distorting factors, as well as the number of participants with missing information for each variable under consideration. In the case of a systematic review or meta-analysis - the characteristics of each study in which the data were used (eg sample size, follow-up);
- information on results: number of participants by categories of main results;
- main results: results of non-adjusted assessment and, if appropriate, adjusted assessment, taking into account distortive factors and their accuracy (eg 95% confidence interval). If appropriate, the relative risk assessment should become an absolute risk for a significant period of time;
- other types of analyzes: other analyzes performed, for example, analysis of subgroups and interactions, as well as sensitivity analyzes;
- adverse events / side effects: management of information on adverse events / side effects and submission of information to the Institution. This should be indicated, especially in the case of specific research designs such as case-control or retrospective cohort studies, systematic reviews and meta-analyzes involving the analysis of electronic medical record data, to assess the reliability of the cause-and-effect relationship at the individual case level.

#### 11.6.3.2.11 Discussion:

- Key findings: key findings related to research objectives; previously conducted research, the results of which correspond to or contradict the current results obtained; if appropriate, the effect of the results on the benefit-risk ratio of the medicine.
- Limitations: limitations of the study that take into account situations that may affect the quality and completeness of the data, limitations of approaches and methods used to minimize their impact (eg, missing or incomplete data, applied estimates), potential errors and inaccuracies, and event reliability sources.
- Interpretation: interpretation of research results, taking into account tasks, limitations, multiplicity of analyzes, results of similar studies and other relevant evidence.
- Generalization: generalization of research results (external reliability).

11.6.3.2.12 Other Information: Any additional or ancillary information about specific aspects of the study that has not been previously considered.

11.6.3.2.13 Conclusion: The main results of the research arising from the analysis of the data.

#### 11.6.3.2.14 References.

The summary of the final results of the study should contain summary information about the research methods and results in the following format:

- 1) Title with subheadings, including the date of the summary, name and details of the first author;
- 2) Keywords (no more than five keywords reflecting the main characteristics of the research);
- 3) Rationale and preconditions;
- 4) Research goals and objectives;
- 5) Research design;
- 6) Terms;
- 7) Patients and size of the study (sample size);
- 8) Variables and data sources;
- 9) Results;
- 10) Discussion (including assessment of the effect of research results on the benefit-risk ratio of the medicine, if appropriate);
- 11) Concluding;
- 12) License holder;
- 13) Name and details of the chief researcher.

### **11.7. Publication of research results by authors**

If the research is conducted in whole or in part by non-licensed researchers and is analyzed, it is recommended that the licensee agree on the publication strategy with the lead researcher in advance. It is recommended that the publication strategy be defined in such a way that, regardless of the authorship of the data, the chief researcher will be able to freely prepare publications based on the research results. In this case, the holder of the certificate must have the authority to review the results included in the manuscript and their interpretations and to comment before the manuscripts are published, avoiding unreasonable delays in publication. Requests for changes to the manuscript must be scientifically substantiated. The cardholder must have the right to request the release of confidential information.

#### **11.7.1. Submission of published research results to the Institution**

The holder of the certificate is recommended to submit the final manuscript of the article to the Institution within two weeks after the publication.

### **11.8. Data protection**

Licensees and researchers must comply with the national legislation on the protection of patients' personal data in the countries where the research is conducted. The holder of the card must ensure that all information about the study is accurately reported, interpreted and verified, and that the confidentiality of the patient's medical records is not compromised.

### **11.9. Quality systems, audits and inspections**

The holder of the license must ensure the fulfillment of pharmacovigilance obligations in relation to the conduct of research, as well as the possibility of audit, verification and verification of this activity.

Any changes to the data must be recorded to ensure tracking. The licensee must ensure that the statistical programs and analytical sets of data used to generate the data included in the final research report are supported in electronic format, as well as that they are accessible for audit and verification.

#### **11.10. Impact on risk management system**

Non-invasive post-registration security surveys (and any intrusive and non-intrusive post-registration surveys in general) conducted to study security issues should be included in the RMP as described in the RMP-related section of this Guide. The research protocol should be attached to the RMP.

In the absence of a RMP, a new RMP containing post-registration security research data should be developed. Appropriate changes will be made to all relevant sections / modules of the RMP, taking into account the conduct of the study, including the safety specification, pharmacovigilance plan and risk minimization plan, as well as a review of risk mitigation measures.

#### **11.11. Mandatory post-registration security research procedure**

If there are concerns about the safety profile of a registered medicinal product, post-registration safety surveys in the Republic of Azerbaijan may be mandatory during the assessment of the first application for state registration or at the post-registration stage. This requirement of the institution should be reliably substantiated by performance and safety profile assessment data, recorded in writing, and include deadlines and assignments for the submission and conduct of research. The requirement may also include recommendations on key research characteristics (eg, research design, conditions, effects, results, target population). Recommended methods include active monitoring methods (eg, monitoring of specific clinical bases, prescription monitoring, registers), comparative observational non-intervention studies (eg, cohort research (monitoring), case-type research, case series research, etc.), may include clinical studies, consumer studies, pharmacoepidemiological studies.

When a post-registration security investigation is scheduled to be conducted at the post-registration stage, the cardholder may request the possibility of providing written observations in response to the commitment within 30 calendar days of receipt of the written notice of the commitment. The agency sets deadlines for the submission of such observations. Based on the written observations provided by the holder of the card, the Institution shall withdraw or confirm the obligation.

#### **11.12. Supervise post-registration security research**

##### **11.12.1. Roles and responsibilities of the card holder**

The holder of the certificate is responsible for ensuring that the research meets the criteria for non-interference research.

Regarding post-registration security research, the licensee must ensure that its pharmacovigilance obligations are met, as well as that it can be audited, verified and verified.

### **11.12.2. Institution**

After the obligation to conduct a post-registration security survey without interference, the licensee shall develop a research protocol and submit it to the Institution for review. Within 60 calendar days from the date of submission of the draft research protocol, the Institution shall approve the draft protocol, recommend making the required changes, refusing to agree or notifying the licensee that the research is under the influence of relevant legislation in the field of clinical research. prepares.

The refusal response must include a detailed justification of the reasons for the discrepancy in each of the following cases:

- it is considered that the research creates conditions for the promotion of medicine marketing;
- it is considered that the research plan does not meet the objectives of the research.

The investigation may be initiated only after the written approval of the protocol by the Institution.

Once the study is started, it is submitted to the Institution until any significant changes are made to the protocol. Within 30 calendar days of submission, the Authority shall evaluate the changes and notify the certificate holder of their approval or rejection.

Upon completion of the survey, the holder must submit the final report on the study, including a summary of the study for publication, to the Institution as soon as possible, but not later than 12 months after the completion of data collection, unless the Authority provides written permission to deviate from the reporting date. . The final report is reviewed by the institution and then the evaluation results are presented to the certificate holder; This result may include additional questions for the cardholder. Based on the review of the report and the possible assessment of the impact of the data on the benefit-risk ratio of the medicine, the Agency recommends changes to the regulatory status of the medicine, recommendations for its application, or other Good measures to ensure the use of medicines if the benefits outweigh the risks. should determine the necessity.

## **12. Security information**

### **12.1. Structures and processes**

#### 12.1.1. Objectives of security awareness

Security information is aimed at:

- timely, scientifically substantiated information on the safe and effective use of medicines;

- assisting in the optimization of medical practice (including self-treatment practice) if necessary;
- changing the existing practice and approaches to the use of medicines;
- support for risk minimization activities;
- Assistance in making informed decisions on the rational use of medicines.

In addition to the above, Good security information helps to strengthen public confidence in the regulatory system.

#### 12.1.2. Principles of security information

The following principles of security information should be applied:

- the need for safety information is taken into account during the implementation of pharmacovigilance and risk management activities. The given component should be part of the risk assessment process;
- it is necessary to ensure Good coordination of activities and interactions between the various parties involved in the creation and exchange of security information;
- Security information should contain relevant, accurate, Good and correct information and be provided to the target audience in a timely manner to ensure that appropriate measures can be taken;
- security information should be tailored to different target audiences (eg patients and medical staff) by using appropriate language, taking into account different levels of knowledge and information requirements, while maintaining the accuracy and relevance of the information transmitted;
- Risk information should be provided taking into account the overall assessment of the benefit of the medicine and contain available and relevant information on the severity, severity, frequency of side effects, risk factors for their development, onset time, reversibility and, if possible, the expected recovery time;
- security information, in particular, should help to eliminate uncertainties in security information, which are relevant in the event of the emergence of new information during the implementation of security information assessment procedures by the Agency; the benefits of informing at this stage should be linked to the risk of error that may arise when it is not possible to properly clarify existing uncertain aspects of the profile;
- Competitive risks should be taken into account when providing safety information, in certain cases, such as the risk of treatment rejection;
- when describing and comparing risks, more reasonable quantitative indicators should be used, for example, indicators of not only relative risks, but also absolute risks; To compare risks, groups should be similar in characteristics. Other methods of presenting information may also be used as a graphical representation of the risk and / or benefit-risk assessment;
- as much as possible, initial consultation or testing should be conducted among healthcare professionals or patients when preparing safety information, especially information on complex safety issues;

- where appropriate, safety information should include the provision of follow-up information, such as subsequent changes to recommendations and solutions to security concerns;
- the effectiveness of safety information should be assessed where appropriate and, where possible;
- security information must comply with the requirements for the protection of personal data.

#### 12.1.3. Target audiences

The main target of safety information provided by the institution and license holders is the medical staff and patients using medicines.

The main target audience is the medical staff. Effective awareness of the safety aspects of medicines allows them to conduct pharmacotherapy with more up-to-date safety information and improved recommendations, as well as to provide patients with clear and useful information, thereby ensuring patient safety and increasing their confidence in the regulatory system and health care system.

The media is also a target audience for security information. The ability of the media to cover patients, health care providers and the general public is an important factor in disseminating new and important information about medicines. Dissemination of security information through the media affects public perception, and it is therefore important for the media to obtain security information directly from the Authority, in addition to information from other sources (eg licensees).

#### 12.1.4. Content of security information

Taking into account the principles given in sub-clause 12.1.2, the safety information shall include the following:

- Important information about any registered medicinal product that affects the benefit-risk ratio of the medicinal product under any application conditions;
- the reasons for initiating the security information procedure in a form understandable to the target audience;
- all necessary safety recommendations for healthcare professionals and patients;
- an indication of the agreement between the holder of the security information certificate and the Institution on the provision of security information, if appropriate;
- details of all proposed changes to the information on the medicinal product (for example, the instructions for use and brief description of the medicinal product);
- a list of references or, where appropriate, references to sources where more detailed information on the information security aspect may be found;
- a reminder of the need to inform the Agency of suspicious side effects through the national spontaneous notification system, as appropriate.

Security information should not be confusing and should be presented objectively. Safety information should not in itself contain any information that may constitute advertising or other information intended to promote the marketing of the medicinal product.

12.1.5. All types of communication tools should be used to deliver security information to target audiences and to meet their growing needs. The various means of communication and information transmission channels that can be used are given in sub-items 12.1.5.1.-12.1.5.5 below.

#### 12.1.5.1. Letter of notification to the medical worker (DHPC)

In this Instruction, a notification letter means that health care providers have provided important safety information directly to health care providers or the Institution in order to inform them about the need to adapt their practice or take specific actions based on new safety information. A health worker notification letter is not a response to a health worker's inquiry.

Development of information material for the letter of notification of the medical worker involves cooperation between the license holder and the Institution. The holder of the card must obtain the consent of the Institution regarding the content of the information material for the notification letter and the information plan for the health worker. The agreement between the institution and the licensee must be completed before the distribution of information materials by the licensee. The consent of the Institution must be obtained in accordance with the information plan and the content of the information, including the target audience and the dissemination schedule. The holder of the card must set aside at least two working days for the submission of comments in response to the comments of the Institution, depending on the content of the information plan or information material. If necessary and if possible, this procedure may be extended for a period of time at the discretion of the Institution; the periods can be adjusted taking into account the urgency of the situation.

When several licensees have to prepare a letter of notification to a health care provider regarding the same active ingredient, it is usually of a single agreed nature.

When preparing information for a health worker's letter of recommendation, it is recommended that, as appropriate, involve as many health organizations or scientific communities as possible to ensure that the information provided is relevant and relevant to the target audience.

The health worker's notification letter may serve as an additional risk mitigation measure for the RMP.

The information for the notification letter to the health worker should be distributed in the following cases when it is necessary to change the existing practice in connection with the medicine or to take urgent measures:

- suspension or cancellation of state registration due to changes in the safety profile of the medicinal product;
- significant changes in the recommendations for the use of the medicine due to changes in the safety profile of the medicine, restrictions on the instructions for use, new contraindications or changes in the recommended doses;

- Restrictions on the availability of medicines or cessation of production, which may adversely affect the system of medical care.

Circumstances in which the need to inform the medical staff should be considered:

- the emergence of new important warnings or special instructions in the recommendations for the use of the medicine;
- new information on the detection of previously unknown risks, as well as the determination of changes in the frequency or severity of known risks;
- the emergence of substantiated information that the medicine is not as effective as previously thought;
- new recommendations to prevent or eliminate the development of side effects, or recommendations to prevent the risks of abuse or medical errors;
- information on the results of regular assessment of important potential risks, the available information of which is not enough to take regulatory measures for a certain period (in this case, the health worker's information letter should help to monitor safety in clinical practice, provide additional impact notices, as well as information on potential risk minimization measures) should give).

The organization has the right to directly disseminate the information for the notification letter to the medical staff or to require the licensee to prepare, agree and disseminate the information for the medical officer's notification letter if it deems it necessary for further safe and effective use of the medicine.

The organization has the right to publish the final version of the information material for the notification letter to the medical worker. The Agency may also, if necessary, disseminate additional safety information to relevant health care organizations and staff.

#### 12.1.5.2. Information for non-specialists

Information material written in simple (non-professional) language (for example, in the format of questions and answers) helps patients and the general public to understand regulatory measures and scientific information related to safety issues. Documents in non-professional language should contain the recommendations and advice of the Institution on risk minimization for health care providers and patients with safety concerns and should be accompanied by relevant reference information.

The agency places information for non-specialists on national medical internet portals and may additionally disseminate it to relevant parties, such as patients and health care organizations.

It is recommended that patients and health care providers be involved in the process of preparing documents in a non-professional language to ensure that the information provided is as relevant and relevant as possible to the target audience.

#### 12.1.5.3. Information in the press

The information published in the press refers primarily to press conferences and press releases intended for journalists.

In addition to posting on the organization's website, it can direct press releases directly to journalists, which will allow journalists to directly access information relevant to the organization's scientific assessment. Interaction with the media is an important way to reach a wider audience, as well as build trust in the regulatory system.

Licensees may also prepare and publish press releases reflecting their position on security issues, but they must include references to all regulatory measures taken by the Authority. Relevant reviews should be included in each piece of information provided by the licensee.

Since press releases can be read not only by journalists but also by other readers, such as medical staff, patients and the general public, they should include references to information materials related to the security issue. It should also be ensured that health workers are informed either before publication or at the same time as the publication or press release is issued, in order to enable health workers to be prepared to answer patients' questions when a health information letter is prepared.

If the issue of security is of great interest to the media, or if it is necessary to bring to the attention of the public a multifaceted and complex information on an important issue for public health, a press conference with journalists can be considered as an effective way to inform the public.

12.1.5.4. The website is an important tool for informing the public (including patients and healthcare professionals). The agency must also ensure that important security information posted on licensee-operated websites is easily accessible and understandable to users. The information on the sites must be constantly updated.

#### 12.1.5.5. Other means of internet communication

Security information can also be shared on the Internet through other web applications. When using the latest, high-speed communication channels, necessary measures must be taken to avoid compromising the accuracy of the transmitted information. In communication practice, new means of communication used by different target audiences must be taken into account.

#### 12.1.5.6. Informational letters and newsletters

Informative letters and newsletters are designed to provide regular updates on medicines and their safety and effectiveness. With the help of these information mechanisms, the Organization can reach a large audience using web applications and other available tools.

#### 12.1.5.7. Interaction between the institution and the competent authorities of other countries

When any of the competent authorities take regulatory action on a specific security issue, it may be necessary for other authorities to respond to inquiries or exchange information on the matter. It is recommended to use inter-regulatory information materials in the format of documents specially prepared by the competent

authorities for the purpose of exchanging information on a specific security issue or cooperating in response to external inquiries.

#### 12.1.5.8. Responding to population inquiries

Institutions and license holders should have a working system for answering individual citizens' inquiries about medicines. Responses should include publicly available information, as well as relevant recommendations provided by the Institution to patients and health care providers. If the questions are related to individual treatment counseling, the patient should be advised to seek medical attention.

#### 12.1.5.9. Other means of data transmission

In addition to the above-mentioned methods of information, there are other tools and channels for the transmission of security information, such as publication in scientific journals and journals of professional organizations.

Some awareness tools and channels can be used in risk management; risk mitigation measures often include specific risk awareness programs. The tools used in these programs, such as a memory book for patients or a safety manual for medical staff, are listed in Section 13.

#### 12.1.6. Effectiveness of security information

Security information is effective when the information transmitted is received and understood by the target audience as intended, as well as when the target audience responds by taking appropriate measures against the information. Appropriate mechanisms based on precise parameters (indicators) should be applied to assess the effectiveness of the data. Based on the effectiveness assessment, conclusions should be drawn, priorities for further awareness-raising activities should be identified, and, if necessary, practices and tools should be aligned to meet the needs of the target audience. A research-based approach should be used to determine whether the safety information meets the requirements of sub-clause 12.1.2. When this approach is applied, different outcomes can be compared, including behavior, attitudes, and knowledge.

Licensees are responsible for the effectiveness of direct informing health workers about safety issues. Licensees should report to the Authority the results of the evaluation of the effectiveness of direct notification, as well as all identified difficulties (for example, problems with the list of recipients or the timing and mechanisms of dissemination). Appropriate corrective and preventive measures should be taken in all cases where the effectiveness of letters informing health workers is found to be insufficient.

#### 12.1.7. Requirements for quality information system for security

In accordance with the requirements set out in Section 3 for the quality of the safety information system, appropriate procedures should be in place to ensure that the safety information complies with the principles set out in sub-clause 12.1.2. Execution and documentation of control procedures related to the transmitted safety information, which in itself is the object of quality control, must be ensured.

## **12.2. Interaction on security information**

### **12.2.1. Requirements for cardholders**

The holder of the license is obliged to inform the competent authority of the country of registration of the medicinal product about the security problems related to the use of the medicinal product or the desire to disclose / disclose to the public information related to pharmacovigilance information. The submission of information to the regulatory authorities for the purpose of notification and approval shall be carried out in advance and at least 24 hours prior to publication before the expiration of the period of restriction on publication. At the same time, informing the Agency by providing information to the public is possible only in exceptional cases and for valid reasons.

At the same time, informing the Agency by providing information to the public is possible only in exceptional cases and for valid reasons.

The cardholder is responsible for the objectivity and accuracy of the information provided to the public.

If the holder of the card receives information that a third party is preparing to disseminate information that may affect the benefit-risk ratio of the medicinal product registered in the territory of the Republic of Azerbaijan, he must notify the Agency.

### **12.2.2. Interaction with third parties**

It is recommended that third parties (eg scientific journals, scientific societies, patient organizations) inform the Agency about any new information on the safety of medicines registered in the territory of the Republic of Azerbaijan and, if this information is planned to be published, inform the Agency before publication.

## **13. Risk minimization measures**

### **13.1. Introduction**

Risk minimization measures are activities aimed at preventing the occurrence of side effects, reducing the frequency or severity of side effects, as well as minimizing the adverse effects on the patient when side effects develop.

The risk mitigation measures included in this section should be reviewed in the context of the main part of the requirements for the risk minimization system (Section 7).

Risk mitigation measures may include routine risk minimization measures or additional risk mitigation measures. Routine risk minimization measures cover all medications and are described in detail in Section 7. Most safety concerns can be reliably managed with routine risk minimization measures, however, for some risks, routine risk mitigation measures may not be sufficient and additional risk minimization measures may be required to ensure Good risk management and / or to improve the benefit-risk ratio of the medicine. . This section provides guidance on the application of additional risk mitigation measures and the selection of risk mitigation tools.

Risk minimization measures are determined based on the security issues presented in the safety specification. Each safety issue should be considered on an individual basis, and the severity of potential side effects, their severity, risk mitigation activities, or instructions for use, route of administration, target populations, and medications should be considered when selecting more appropriate risk mitigation measures. The type of health care facility to which the medicine is applied should be taken into account. A security problem can be considered in more than one risk minimization measure, and a specific risk minimization measure can cover more than one security problem.

The holder of the license is responsible for ensuring Good control over the implementation of risk minimization measures included in the RMP agreed with the Authority or as a condition for state registration.

The agency is responsible for verifying the results of the application and implementation of risk mitigation measures included in the RMP or identified as a condition for state registration.

## **13.2. Structures and processes**

### **13.2.1. General principles**

Risk minimization measures are aimed at optimizing the safe and effective use of the medicine throughout the life cycle. The benefit-risk ratio of the medicine is determined by minimizing the severity and risks of subsequent side effects, as well as targeted selection and / or patient exclusion or careful monitoring of treatment (eg, specific admission regimen, appropriate laboratory monitoring, follow-up of patients, etc.) can be improved by optimizing the benefits. Risk minimization measures are taken to ensure the optimal use of the medicine in medical practice by a specialist who has the necessary training for the specific patient at the right time, at the right dose, prescribing and treating patients, as well as with Good information and Good control. should form a leadership.

There are a number of different methods used as additional risk minimization measures. This section of the regulation of the circulation of medicines is under continuous development, and existing methods will be complemented by new ones, including those aimed at the wider use of Internet technologies.

Successful implementation of additional risk mitigation measures requires the contribution of all parties, including licensees, patients and healthcare professionals.

Additional risk management measures should have a clearly defined goal in line with the overall objectives of minimizing specific risks and / or optimizing the benefit-risk ratio. Predetermined assessment parameters for achieving specific goals and key objectives should be guided by the development of additional risk mitigation measures. Good monitoring should be provided during the application phase, as well as during the process for performance and for pre-defined parameters after completion of the procedure. Characterization of the safety

problem in the context of the clinical activities necessary to minimize risk, target populations, therapeutic value of the medicine and the benefit-risk ratio of the medicine, selection of risk minimization strategies and risk minimization tools / methods to ensure desired public health outcomes are factors to consider. Regular interim assessments of the effectiveness of risk mitigation measures should be aimed at the timely detection of their ineffectiveness and the application of appropriate corrective measures.

The risk minimization plan is an integral part of the RMP. The risk minimization plan should include the following sections:

- Rationale for the need to apply additional risk mitigation measures (related to specific security issues): this section should justify the proposed additional risk mitigation measures, which should include specific objectives for each proposed measure. A clear description of how the proposed additional risk mitigation measure is aimed at a specific security problem should be provided;
- Description of additional risk mitigation measures: this section should provide a description of the additional risk mitigation measures selected, as well as a description of the tools / methods and key components to be used.
- Implementation plan: this section should provide a detailed description of proposals for the implementation of additional risk minimization measures (eg, characteristics of interventions, detailed information about the target audience, curriculum implementation and / or training distribution plan, if appropriate, other licensees of the measures coordination mechanism with);
- Assessment plan: This section should provide a detailed plan with key steps to assess the effectiveness of additional risk mitigation measures in terms of the implementation of the planned process and overall indicators of impact on outcomes (eg risk reduction).

#### 13.2.2. Risk minimization measures

Additional risk minimization measures are proposed when assessed as a condition for safe and effective use of the medicine. The proposed additional risk mitigation measures should be scientifically substantiated, developed and submitted by qualified professionals.

Additional risk minimization measures can have different purposes, design, target audience, and complexity. These measures are aimed at controlling important risks and/or ensuring Good monitoring of treatment in relation to the Good management of side effects in the event of their development, in order to ensure Good procedures for selecting appropriate patients whose benefits outweigh the risks can be used. In addition, specific risk mitigation measures may be developed to ensure a Good prescribing of the medicine and / or to the risks associated with medical errors, in cases where this is practically impossible to achieve only by providing information about the medicine in the instructions for use or on the label.

If a request is made for additional risk minimization measures, the rationale for the request should be documented, as well as specific security issues should be

identified and detailed planning for the implementation and assessment phases should be provided.

Additional risk minimization measures may include:

- curriculum;
- controlled access program;
- other risk mitigation measures.

#### 13.2.2.1. Curriculum

Many risk mitigation tools/methods that can be used in the curriculum are based on targeted information by providing information contained in the instructions for use and brief description of the medicine. Any training material should be aimed at achieving certain risk minimization goals and should contain accurate and specific information.

The aim of the training program is to optimize the use of medicines by positively impacting the activities of health workers and patients in minimizing risks. The training materials should be based on the assumption that there is a practical and effective recommendation for targeted awareness and that the application of the given measure is important and significant for minimizing significant risk and / or optimizing benefit-risk ratio. The teaching tools used in the context of the curriculum can have several different target audiences, focus on more than one security issue, and can be transmitted using a combination of tools and media (on paper, audio, video, internet, individual learning). It is recommended that materials be presented in a variety of formats to ensure accessibility, including in the event of a media outage or access to the Internet.

The content of any training material must be fully consistent with the validated information on the medicinal product, such as the instructions for use and a brief description of the medicinal product. Direct or covert advertising elements should not be included in the content. The training materials should focus on medicine-related risks and the management of such risks that require additional risk minimization measures.

Any training program should be completely isolated from advertising activities, and contact information of doctors and patients obtained with the help of the training program should not be used for advertising purposes.

When developing a curriculum for additional risk minimization purposes, the teaching tools described below may be considered individually or in combination.

##### 13.2.2.1.1. Teaching tools

Teaching aids should have a clearly defined direction and include an unambiguous definition of the risk to the problem under consideration, the nature of the risk (s) and the measures to be taken by health care providers and / or patients to minimize such risks. This information should focus on well-defined activities related to specific security issues in the risk minimization plan and should not contain information that is not directly related to the security problem, as well as reliably

presented in the operating instructions or brief description. Information elements for inclusion in teaching aids/methods may include:

- instructions on the appointment of the medicine, including control and monitoring aimed at minimizing the significant risks of selection, patient selection;
- instructions on the management of such risks (for medical staff, patients or caregivers);
- instructions for providing information on identified side effects of particular interest to characterize a particular risk.

#### 1) teaching tools/methods for medical staff

The purpose of any training tool/method for health care workers is to use (what should be done) and/or contraindications (what not to do) and/or to take precautions that require additional risk minimization measures, including: is the presentation of specific aspects of the recommendations for measures (how to manage side effects):

- selection of patients;
- treatment methodology, dosing regimen, control and monitoring;
- special administrative procedures or release of medicines;
- Detailed information to be provided to patients.

The choice of the format of the teaching tool/method depends on the information provided. For example, if it is necessary to perform a certain number of activities before prescribing an individual patient, the checklist may be in an appropriate format. The brochure format may be more appropriate for professionals to recognize specific risks, with an emphasis on early detection and management of side effects, while posters may contain useful therapeutic guidelines or medication regimens. Other formats can be chosen depending on the amount, direction, target audience and other factors of the information.

#### 2) Teaching tools/methods for patients and caregivers

Teaching tools/methods for the patient should be aimed at improving the understanding of patients and caregivers of signs and symptoms that are important for early detection of specific side effects that require additional risk minimization measures as well as optimization of the patient's subsequent treatment. If appropriate, the teaching tool/method should be recorded or performed by the patient in further discussion with health care providers to ensure that information is provided to the patient and that important steps, such as the steps required for effective medicine administration, are followed. can be used to remind you to take notes.

##### - Memory book for the patient

The purpose of this tool is to ensure that specific information about the patient's current treatment and associated risks (such as potential interactions with other medications) is always available to the patient and available to the appropriate health care provider. The information should include basic risk minimization

guidelines and, in any case, the necessary mitigation measures, including the minimum necessary for the transmission of emergency measures.

#### 13.2.2.1.2. Controlled accessibility program

The controlled access program consists of operational measures aimed at controlling access to a medicine beyond the level of control guaranteed by the standard risk minimization measures, ie the regulatory status of the medicine. Controlled accessibility should be considered as a serious risk minimization method for a medicine with proven benefits that cannot be achieved without additional risk minimization measures due to the risk to patients' health.

The requirements to be met before a medicine is prescribed and / or released and / or used in a controlled access program are, for example, listed below (they may be included individually or in combination with other requirements):

- patient-specific examination and / or examination methods to ensure compliance with strictly defined clinical criteria;
- the doctor prescribing the medicinal product, the pharmacist dispensing the medicinal product and/or the patient confirm in writing that they have received and understood the information regarding the serious risk of using the medicinal product;
- Precise procedures for subsequent systematic observation of the patient in a special data collection system, for example, with the help of patient registry systems;
- medicines can be obtained only from pharmacies licensed to sell such medicines.

In certain cases, the requirements for a special examination or monitoring of the patient's condition may be used as a controlled access tool. For example, checking the patient's condition before and/or during treatment, laboratory tests or other characteristics (eg, ECG), monitoring liver function parameters, regular blood tests, pregnancy tests (which may be part of a contraception program). Measures should be taken to ensure compliance with the instructions for use when there is a critical factor in terms of the benefit-risk ratio of the medicine.

#### 13.2.2.1.3. Other risk minimization measures

##### 1) Pregnancy prevention program

A contraceptive program is a set of measures aimed at minimizing the risk of fetal exposure to a medicine with known or potential teratogenic effects during pregnancy. The program should ensure that female patients do not become pregnant at the beginning of treatment or become pregnant during the course of treatment and/or for a certain period after the end of treatment. Also, if taking the medicine by a biological father may adversely affect the outcome of the pregnancy, the contraception program may also target male patients.

The contraceptive program combines the use of teaching aids and appropriate access control tools. For this reason, the following elements should be considered both individually and together when planning a contraception program:

- teaching aids for health care providers and patients to inform them about teratogenic risk and given risk minimization measures, such as instructions on the use of multiple contraceptives and instructions on different types of contraception; information for the patient regarding the duration of the period during which the pregnancy should be avoided after the end of treatment;
- controlled access to the level of prescribing or dispensing of the medicine by ensuring that the pregnancy test is performed and the negative results are checked by a health worker or pharmacist before prescribing or dispensing the medicine (s);
- Limiting the validity of the prescription to 30 days;
- Consultation in case of unplanned pregnancy and assessment of the outcome of any accidental pregnancy.

Consideration should also be given to the appropriateness of the application and design of the pregnancy register to record data on all female patients who became pregnant during treatment or at an appropriate time after treatment, for example within 3 months.

## 2) Letter of notification to the medical staff

A letter of notification to a healthcare professional is a serious safety statement made directly by a licensee or the Institution to certain health care providers in order to minimize specific risks and/or to minimize the severity of side effects of the medicine, to harmonize accepted medical practice and/or to take serious measures is an active form of information-mediated information. (see Section 12).

### 13.2.3. Implementation of risk minimization measures

Additional risk mitigation measures may include one or more active measures to be applied and implemented in a specific target audience. Due attention should be paid to both the time frames for the implementation of risk minimization measures and the procedures aimed at achieving the goals in the target group. For example, a one-time implementation of training tools/methods “before launch” may not be sufficient to cover consumers and/or prescription physicians. There may be a need for additional periodic redistribution of tools/methods after the implementation of the program. Due attention should be paid to the general format of teaching aids/methods to ensure that they are clearly distinguished from any type of promotional material. The submission of training materials to the Institution for approval shall be carried out separately from the submission of promotional materials, in which case the accompanying letter shall indicate whether the materials are intended for advertising or teaching. Training materials should be distributed separately from advertising materials, which should indicate that the material is not for advertising. Quality assurance mechanisms should ensure that distribution mechanisms are in line with the intended purpose of risk mitigation measures and are controlled.

### 13.2.4. Effectiveness of risk minimization measures

Assessing the effectiveness of risk mitigation measures is the basis for determining the effectiveness of active risk mitigation measures, the reasons for their

ineffectiveness, as well as the need for corrective measures. Effectiveness is assessed for each risk minimization measure and for the program as a whole.

The effectiveness assessment should take into account various aspects of the risk mitigation measure: the process itself (ie, the level of implementation of the planned program), its impact on awareness and changes in the target group's behavior, as well as the outcome (ie, short- or long-term risk mitigation goals). level of achievement). The timing of the assessment of each aspect of the active measure should be thoroughly planned within the risk management plan prior to the commencement of the measures.

Two groups of indicators should be used to assess the effectiveness of risk minimization measures:

- process indicators;
- result indicators.

Process indicators are important for gathering evidence of the successful implementation of all phases of risk minimization measures. This group of process indicators should provide an assessment of the level of implementation of the planned program and the achievement of the desired impact on the behavior/activities of the target group. Program performance should be predetermined and monitored throughout the program. The experience and information gained can be used to optimize corrective action if necessary. Assessing process performance can also improve an understanding of the process and causal mechanisms that allow additional risk minimization measures to control specific risks as desired.

Outcome indicators provide an overall assessment of the level of risk control achieved through the application of risk mitigation measures. For example, if the goal of an operational measure is to reduce the incidence and/or severity of an adverse event, the ultimate success indicator will be relevant to that goal.

Based on the results of the risk mitigation measures evaluation procedures, a decision is made on the possibility of further implementation of the assessed risk mitigation measure or the need to change the activity. Evaluate the effectiveness of a risk mitigation measure to determine whether risk mitigation activities are insufficient and need to be strengthened (e.g. with improvement) may indicate. Another outcome of the assessment procedure is the identification of non-compliance of risk mitigation measures or the lack of targeting required, which may be considered to reduce or simplify the workload of the program (for example, by reducing the number of risk mitigation tools/methods or frequency of elements) .

In addition to assessing the effectiveness of risk mitigation measures in the management of safety concerns, it is important to assess whether the population may have unintended (negative) consequences in the near or long term over the health problem in question.

#### 13.2.4.1. Process indicators

Process indicators are parameters for evaluating the volume of implementation of the initial program and/or changes in its implementation. Process indicators should not replace, but complement, the assessment of achievement of objectives by implementing risk minimization measures (ie, outcome indicators). Depending on the nature of the active measures, different process indicators can be identified to assess their effectiveness.

#### 13.2.4.1.1. Delivery to the target population

Where risk mitigation measures include the provision of information and guidance to health care providers and/or patients through teaching methods, information dissemination assessment measures should be used to obtain key procedural information. These indicators should be aimed at assessing the appropriateness of the target audience's tool used (eg, appropriate language, drawings, diagrams, or other graphical support) or the actual acquisition of materials by the target group.

#### 13.2.4.1.2. Assessment of clinical knowledge

Strict scientific methods of analytical inquiries should be applied in order to assess the level of knowledge and awareness of the target audience obtained through operational training activities and/or through the presentation of information (for example, through the instructions for use of the medicine).

Typically, an analytical questionnaire includes basic standard questions that are given over the phone in a personal interview or independently sent by mail/email, repeated from time to time. Such an approach can be adapted to assess attitudes and awareness in representative groups of patients and/or health professionals through appropriate psychometric values. In order to perform the assessment, an adequate sample size should be determined using the randomization method.

Due attention should be paid to the objectives of the analytical survey, the design of the study, the sample size and representation, the operational definitions of dependent and independent variables, as well as statistical analysis. Care should also be taken to select more appropriate data collection tools (eg questionnaires, questionnaires).

#### 13.2.4.1.3. Evaluation of clinical activities

In order to assess the effectiveness of operational training measures and/or information support, not only clinical knowledge but also knowledge-based clinical activities (eg, prescribing) should be identified. Research on the use of medicines with the secondary use of electronic medical records should be considered as a valuable tool for quantifying the clinical activities of the target group. In particular, the analysis of medicine prescriptions in conjunction with other patient data (eg, clinical and demographic data), evaluation of medicine prescriptions, including the identification of two medicines with interactions, compliance with laboratory monitoring recommendations, and patient selection and their can provide control over the condition. Appropriate statistical methods can be used to assess various aspects of the prescribing or application of medicines

for cohorts of medicine consumers, which can only be understood within the framework of descriptive evidence.

#### 13.2.4.2. Outcome indicators

An indicator of the ultimate success of a risk minimization program is the safety outcome, i.e., the frequency and/or severity of side effects associated with the effects of medications on the patient outside the scope of the intervention (ie, non-intervention study). The assessment based on these indicators should include a comparison of the epidemiological measures of the frequency of the outcome as an indicator of the frequency or cumulative frequency of additional effects obtained in the context of safety studies at the post-registration stage. In accordance with any approach, strict scientific and accepted principles of epidemiological research should always be followed to evaluate the final outcome indicator. Frequency comparisons should be considered before and after risk minimization measures are taken. If it is practically impossible to carry out assessments and calculations before and after the measures are taken (for example, risk minimization measures came into force upon registration), retrospective data on patients' e-cards with a predetermined reference value from literature sources, is correlated with the expected frequency in the general population (e.g., an analysis observed compared to the proposed analysis) and should take into account the possible effect of notification stimulation. The choice for the comparison group must be reliably justified.

Spontaneous notification level (ie, number of notifications of suspected side effects over a fixed period of time), acceptable assessment of the incidence of side effects in the treated population, except in special cases where the underlying frequency of side effects is insignificant and there is an interaction between treatment and side effects should not be considered as. In cases where it is practically impossible to determine the level of risk in the group under consideration, spontaneous notifications may provide a rationale for the approximate value of the frequency of side effects in the group, provided that some reasoned information is obtained to assess the level of notification in the context of medicine administration. However, characteristic errors that affect the notification level in relation to possible side effects can lead to confusing errors. For example, the implementation of a risk minimization program in response to a safety problem identified during post-registration monitoring of a medicine may help increase awareness of specific side effects, which may ultimately lead to an increase in the notification rate. In such cases, the analysis of the spontaneous notification may lead to the erroneous conclusion that the intervention is ineffective. Decreased reports over a period of time can also lead to the erroneous conclusion that the intervention is effective.

#### 13.2.5. Coordination

If there are several medicines on the market, including those with the same active ingredient, a unified approach to the application of additional risk mitigation measures provided by the Agency should be developed. When there is a need for

coordinated action in relation to a group of medicines, a coherent approach should be developed. In such situations, initial planning should ensure that the effectiveness of risk minimization measures is assessed for each individual medicine, as well as for the medicine as a whole.

#### 13.2.6. Quality systems of risk minimization measures

Although many experts may be involved in the development and implementation of risk mitigation measures, the ultimate responsibility for the quality, accuracy and scientific completeness of such measures rests with the licensee and the person responsible for pharmacovigilance in the Republic of Azerbaijan.

The cardholder is responsible for updating the RMP in the event of new information, as well as applying the quality principles set out in detail in Section 3. Tracked versions of RMP should be submitted to the Authority for review and evaluation. Submitted reports, RMPs and risk management systems included in the plan may be audited or audited as are any documents related to risk mitigation measures.

The licensee must ensure that the reporting mechanisms based on the results of analyzes or studies to assess the effectiveness of risk mitigation measures are documented. These documents may be audited and audited.

### **13.3. Responsibility of the institution**

The agency is responsible at the national level for the implementation of additional risk minimization measures identified as a condition for the safe and effective use of medicines.

In connection with the risk mitigation measures applied after the issuance of the registration card, the Authority shall ensure the operative review of the submitted measures and coordination with the license holder.

If necessary, the Agency may assist in agreeing on risk minimization measures for generic medicines containing the same active ingredient. Where there is a need for additional risk mitigation measures for generic medicines due to the safety of the active substance, the risk mitigation measures applied to generic medicines should be aligned with the risk minimization measures for the original medicine. In specific situations, in addition to the risk minimization measures applied to the original medicine, additional risk minimization measures may be required for hybrid medicines (for example, due to differences in composition, method of administration, or incompatibility problems).

The entity shall ensure the application of each risk minimization tool/method. The organization shall discuss with the applicant/licensee the format and means of risk minimization tools/methods, including printed materials, Internet platforms and other audio-video means, as well as planning (schedule) of operational measures before the medicine is put on the market or at any other time if necessary must agree.

The body makes an independent decision on the selection of appropriate national training materials and/or other tools / methods for risk minimization. The agency monitors the results of the implementation of risk minimization measures at the national level.

#### **13.4. Responsibilities of cardholders**

The cardholder must clearly define the objectives of the proposed additional risk mitigation measures and the indicators for assessing their effectiveness. Any additional operational risk mitigation measures shall be developed in accordance with the general principles set out in sub-paragraphs 13.2.1 and 13.2.2 and shall be fully documented and approved in the risk minimization program (see Section 7).

The measures approved by the agency in the risk minimization plan should be implemented at the national level. The holder of the license must provide information on the status of implementation of additional risk mitigation measures in accordance with the initial agreement with the Agency, as well as inform the Agency about any changes, difficulties or issues arising during the implementation of additional risk mitigation measures. Any relevant changes to the tools / methods of implementing risk mitigation measures shall be agreed with the Institution prior to the entry into force of these changes.

When using tools/methods based on Internet technologies, the licensee must apply the requirements in force in the territory of the Republic of Azerbaijan, taking into account the potential problems with the accessibility, recognition, responsibility, confidentiality and protection of information.

In connection with generic medicines, the license holder must develop risk minimization measures in accordance with the scope, direction, content and format of the tools/methods applied to the original medicine. Scheduling and operational planning must be coordinated reliably to minimize the burden on the health system. Evaluation of the effectiveness of risk minimization measures in relation to generic medicines should be carried out by the licensee in close cooperation with the Agency. Joint research is strongly recommended if research is justified to minimize the burden on the health system. For example, if a prospective cohort study is scheduled, the inclusion in the study should not depend on the designation of the medicine with a particular trade name or the specific manufacturer of the medicine. In such cases, it is important to record the data of a particular medicine in order to quickly identify any new risks specific to a particular medicine.

The licensee must monitor the results of the risk mitigation measures included in the risk management plan. The general principles of performance appraisal are set out in sub-clause 13.2.4 of this section.

The holder of the certificate must submit a report on the evaluation of the effectiveness of additional risk mitigation measures related to the assessment of the benefit-risk ratio in the PSUR.

The holder of the certificate must ensure that the Institution is contacted in a timely manner to carry out the relevant regulatory assessment and activities.

### **13.5. Medical staff and patients**

The collaboration of health professionals and patients is a critical factor in the successful implementation of a controlled accessibility program and/or training program to optimize the benefit-risk ratio. It is desirable that they pay due attention to any risk mitigation measures that can be applied to ensure the safe and effective use of medicines.

### **13.6. Impact of risk minimization measures on RMP / PSUR**

Updates to PSUR and RMP should include an overall assessment of the results of additional risk mitigation measures applied to reduce significant risks associated with the use of medicines. Attention should be paid to how the activities carried out in the RMP and its results are reflected in the planning of the RMP and/or pharmacovigilance. The impact of the measures applied in the PSUR on the safety profile and/or benefit-risk ratio of the medicine should be assessed. In general, information obtained during the reporting period or at the time of the most recent risk mitigation measures should be highlighted.

The results of the assessment of the effectiveness of risk minimization measures should be included in the RMP in all cases. As part of such a critical assessment, the licensee should observe the factors that contribute to the achievement of the objective or, conversely, the inadequacy/ineffectiveness of risk mitigation measures. If such a critical analysis is available, it may include a reference to experiences outside the territory of the Republic of Azerbaijan.

When evaluating the effectiveness of risk minimization measures, it should be emphasized whether they are successful in minimizing target risks. The assessment shall be performed using a combination of process and outcome indicators as described in sub-clause 13.2.4. It is recommended that a boundary be established between the risk mitigation measures applied and the measures taken in the post-registration period when issuing the state registration certificate.

Evaluation of the effectiveness of risk minimization measures should be provided taking into account the following recommendations:

- The assessment should present the context in the following ways:
  - a) a brief description of the risk mitigation measures applied;
  - b) defining their purpose;
  - c) a description of the selected process and its outcome indicators.
- The assessment should include an appropriate analysis of the nature of the side effects, including their severity and prevention. Where appropriate, logistical factors that may affect the clinical implementation of risk minimization measures should also be included;

- The assessment should include a study of the implementation of risk minimization measures in regular clinical practice, as well as all deviations from the initial plan. This assessment may include the results of research on the use of the medicine;
- Outcome indicators (ie frequency and / or severity of side effects) should, as a rule, be the main endpoints when assessing the level of achievement of the set goals when implementing risk minimization measures;

Proposals for changes to improve risk management measures should be submitted in the relevant section of the PSUR. The risk minimization plan should be updated to take into account the information received on the effectiveness of risk mitigation measures.

The frequency of RMP renewal should be commensurate with the risks of the medicine. In general, RMP updates should focus on providing updates on risk mitigation measures and a risk minimization plan, if appropriate. In case of renewal of a limited number of sections, the affected sections should be listed in the cover letter when submitting the documentation. Where changes to the operating instructions are required as a result of the implementation of risk minimization measures, the justification and details of the changes shall be confirmed by the submission of a PSUR reflecting the specified aspects.

### **13.7. Transparency**

The agency ensures the transparency and accessibility of information on risk mitigation measures by placing information on relevant Internet portals (for example, existing operating instructions, etc.).

## **14. Special control (Additional monitoring)**

### **14.1. Introduction**

Pharmacovigilance is a vital function of the health care system, as it aims to quickly identify and respond to potential safety hazards related to the use of medicines.

State registration of a medicinal product is carried out on the basis of a positive benefit-risk ratio at the time of registration of the medicinal product within the approved instructions (s) and recommendations for use for certain target groups of patients. However, not all risks may be detected for the first time of registration, some risks are identified at the post-registration stage, during the widespread use of the medicine throughout its life cycle. In order to ensure the feasibility of medicine safety testing in proportion to the level of risks associated with its use, it is advisable to develop a list of medicines that require extensive collection of safety information after registration, which implies the application of special medicine control (additional monitoring). .

The agency prepares a single list of medicines under special control (additional monitoring) (hereinafter - the List), maintains and publishes at the current level. In

the instructions for use and brief description of these medicines, “This medicine should be specially monitored. This will allow you to quickly identify new security information. Medical personnel are asked to report any suspected side effects. See "Reporting side effects". The explanatory standard is represented by the inverted black triangle symbol ▼, accompanied by the text. Also, the following text should be included in the "Side effects" section of the instructions for use and brief description of the medicine:

#### Reporting side effects

If you experience any side effects not listed on this leaflet, tell your doctor or pharmacist. Information on side effects during the use of medicines should be reported to the Center for Analytical Expertise of the Ministry of Health of the Republic of Azerbaijan (indicating the address, fax, e-mail, telephone number of the Center). By providing information about side effects, you are helping to gather more information about the safety of this medicine.

## **14.2. Structures and processes**

### 14.2.1. Principles of granting special control status to a medicine

Registration of all medicines is based on the acceptance of a positive risk-benefit ratio, taking into account the data available at the time of registration (data from clinical trials/experiments conducted during the development of the medicine). However, side effects that rarely occur or occur during long-term use may be identified after the medicine has been used by a wider patient population or after long-term use. In addition, the benefits and risks associated with the medicine may be assessed under conditions different from those of daily medical practice; for example, clinical trials/trials may exclude certain types of patients with multiple co-morbidities or taking concomitant medications. Thus, once a medicine is on the market, its use by different population groups requires constant monitoring. Licensees and the Authority carry out regular monitoring of medicines to obtain safety information, as well as assess their impact on the benefit-risk ratio of the medicine. However, some medicines require more intensive collection of safety information after state registration in order to detect each new, significant security problem as quickly as possible and to take immediate and Good action. The concept of special control (additional monitoring) has been proposed to increase the effectiveness of monitoring the safety of certain medicines and to stimulate more intensive provision of spontaneous notifications of identified side effects.

The status of special control (additional monitoring) of a medicinal product may be granted upon issuance of a state registration certificate or at a later stage of the medicinal product life cycle, when a new safety problem is detected in the post-registration monitoring process. The status of special control (additional monitoring) is especially important when issuing a registration certificate for all medicines of biological origin, a medicine containing a new active substance, which is a priority for the implementation of pharmacovigilance. The Authority

may also require that special control (additional monitoring) status for medicines be applied in certain circumstances, for example, based on the results of post-registration safety studies or when there are restrictions on the safe and effective use of the medicinal product.

#### 14.2.2. Information exchange and transparency

The status of special supervision (additional monitoring) should be conveyed in such a way that the number of notifications of possible side effects to health care providers and patients will increase, but this will not cause excessive anxiety. This can be achieved, for example, by emphasizing the need to better characterize the safety profile of a new medicine by identifying additional risks, but by linking these potential risks to the proven benefits and therapeutic benefits of a given medicine. The general list of available medicines with special control (additional monitoring) status should be constantly updated by the Agency. In addition, healthcare professionals and patients should be able to easily identify these products by their labeling. The publication of the list, together with the relevant notification, should prompt medical personnel and patients to report any suspected side effects of the medicines under special control (additional monitoring).

### **14.3. Criteria for inclusion of the medicine in the list of special control (additional monitoring)**

#### 14.3.1. Mandatory admission criteria

The list of medicines under special control includes the following categories of medicines:

- medicines containing a new active ingredient registered in the territory of the Azerbaijan Republic, which were not registered in the territory of the Azerbaijan Republic before the entry into force of the Decision;
- medicines of biological origin registered in the territory of the Azerbaijan Republic after the decision comes into force;
- medicines required for post-registration safety research by the Agency upon issuance of a state registration certificate or after the issuance of a state registration certificate;
- the medicine is on the list of medicines under special control in international practice.

#### 14.3.2. Additional (optional) inclusion criteria

At the request of the institution, medicines may be included in the list of medicines under special control (additional monitoring) based on the following additional inclusion criteria:

- Recommendations for the use of the medicine contain significant restrictions necessary to ensure its safe and effective use;
- The use of measures to ensure the safety of medicines in the risk management system has been identified by the organization;

- The institution has established an obligation for the license holder to conduct post-registration performance studies.

The decision to include the medicinal product in the list of medicinal products under special control (additional monitoring) should also take into account the appropriateness of this status, taking into account other additional pharmacovigilance measures proposed in the RMP.

#### **14.4. Criteria for determining the initial timing of amendments to the list of medicines under special control (additional monitoring)**

##### **14.4.1. Mandatory criteria**

The initial entry period for medicines containing a new active ingredient, as well as for all medicines of biological origin, is five years from the date of state registration in the territory of the Republic of Azerbaijan.

##### **14.4.2. Additional criteria**

For medicines included in the list under certain conditions, the period of inclusion in the list is related to the fulfillment of the relevant obligations and conditions imposed on the licensee and is determined by the Agency in accordance with their implementation and the results obtained.

During the life cycle, the medicine can be included in the list of medicines under special control (additional monitoring) more than once.

#### **14.5. Obligations of the institution**

The organization must:

- prepare a list of medicines registered in the territory of the Republic of Azerbaijan, under special control (additional monitoring);
- when determining the frequency and characteristics of the procedures performed for the detection of signals, should take into account the list of medicines under special control (additional monitoring);
- inform the relevant licensee about the decision to include in the list of medicines under special control (additional monitoring);
- take necessary measures for medical staff and patients to report any suspicious side effects of the medicine included in the list of medicines under special control (additional monitoring);
- update the list of medicines under special control (additional monitoring).

#### **14.6. Obligations of cardholders**

The holder of the card is obliged to perform the following:

- to include a black triangle symbol *qısa*, as well as an explanatory standard text on additional monitoring in the instructions for use and brief characteristics of medicines included in the list of medicines under special control (additional monitoring);

- to include information on the status of special control (additional monitoring) in each material to be distributed among medical staff and patients, as well as to make every effort to stimulate the reporting of additional effects, as agreed with the Institution;
- to submit to the Institution the confirmation of the status of fulfillment of any conditions imposed on it by the Institution and relevant information;
- to submit relevant changes to the instructions for use and brief description of the medicinal product for the input / output of the black symbol and the explanatory standard text in the manner prescribed by law.

#### **14.7. Black characters and explanatory standard text**

The list of medicines under special control (additional monitoring) must contain an inverted black triangle symbol ▼ inverted in the instructions for use and brief description of the medicine, which must be accompanied by the following explanatory standard text:

"This medicine needs special control. This will allow you to quickly identify new security information. Medical personnel are asked to report any suspected side effects. See the section on informing about the side effects of the medicine.

After the medicinal product has been added to or removed from the list, the licensee is obliged to make appropriate adjustments to the instructions for use and brief description of the medicinal product to include or remove the black symbol, application and explanatory standard text, depending on the situation. If the decision to add or remove a medicine from the list is made within the framework of regulatory procedures (eg state registration/re-registration procedures, procedures for making changes to the medicine's instructions for use), the inclusion of a black triangle and explanatory standard text in the medicine information and or the content of the instructions for use and brief description shall be updated prior to the completion of the procedure in order to extract this information. If the decision to include or remove a medicinal product from the list is made outside the scope of normative procedures, the licensee shall be obliged to make appropriate changes to the instructions for use and brief description in accordance with the legislation.

#### **15. Procedure for examination of pharmacovigilance documents of medicines (RMP, PSMF and PSUR)**

15.1. For the purpose of examination of pharmacovigilance documents (RMP, PSMF and PSUR) during the period of validity of the registration certificate of the medicinal product after the state registration of the medicinal product, the licensee (or the legal entity authorized by him) (hereinafter the Applicant) The contract is concluded in accordance with paragraph.

15.2. The applicant must apply to the Institution within 15 (fifteen) working days from the date of issuance of the certificate of state registration of the medicinal

product in the form provided in Annex 1 to this Instruction. If the applicant is a person authorized by the cardholder, a document confirming his/her authority must be submitted together with the application. Upon receipt of the application by the Institution, the Institution shall provide the applicant with a written or electronic notification and a contract form.

15.3. Upon receipt of the notification, the applicant within 5 (five) working days concludes an agreement with the Agency on the examination of pharmacovigilance documents. Within 5 (five) working days after the conclusion of the contract, the Agency shall submit an invoice for payment of the cost of the examination in accordance with the contract.

15.4. Within 15 (fifteen) working days after submission of the invoice, the applicant must pay the cost of the examination to the bank account of the Institution.

15.5. Examination of pharmacovigilance documents of a medicinal product shall be carried out in accordance with the type of document within the following periods:

15.6. Within 45 (forty five) business days for RMP;

15.7. Within 60 (sixty) working days for PSUR;

15.8. Within 60 (sixty) working days for PSMF;

15.9. If during the examination of each document inconsistencies and errors are found in the documents submitted by the applicant, as well as if the information in these documents is not sufficient for examination, the Agency shall notify the applicant in writing within 5 (five) working days. The applicant must ensure the elimination of errors and inconsistencies and provide the required additional information within 60 (sixty) calendar days, and this period does not apply to the period of the examination.

15.10. If the applicant does not eliminate the errors and inconsistencies within 60 (sixty) calendar days or does not provide the required additional information, the examination shall be suspended. The Ministry shall be notified of this in writing within 5 (five) working days and in accordance with the requirements of sub-clause 19.6 of the Rules. The submitted documents and the cost of the examination are not returned to the Applicant.

15.11. The institution has the right to request the applicant to provide additional information only 1 (one) time in relation to each document in accordance with paragraph 15.4 of this Instruction.

15.12. As a result of the examination, based on the results of the pharmacovigilance evaluation of the documents, the applicant shall be provided with Risk “Management Plan (RMP)” 2, “Periodically Renewed Safety Report (SRS)” 3 and “Main Pharmacovigilance File (FSA)” in accordance with this Instruction. Expert opinions shall be submitted in the form provided for in Annex 4.

15.13. The provisions of paragraph 19.7 of the Rules shall apply if an opinion is issued that the documents submitted for examination do not comply with the requirements of the Rules and this Instruction.

To the Instruction to Good Pharmacovigilance Practice (EFT)  
Appendix No. 1

## **On examination of pharmacovigilance documents of medicines**

### **Application form**

\_\_\_\_\_  
(title of the state body (institution) carrying out the examination)

\_\_\_\_\_  
(title of the applicant organization, organizational and legal form)

\_\_\_\_\_  
(registration date, number, TIN, bank details, legal address of the applicant organization)

\_\_\_\_\_  
(surname, name, patronymic, place and position of employment, address, number of identity document, date of issue and name of the issuing authority)

### **Application**

\_\_\_\_\_  
(title, dose, dosage form of the medicine)

We ask you to conduct an examination of pharmacovigilance documents.

Applicant

official of the organization \_\_\_\_\_

(surname, name, patronymic) (signature)

P.S.

Date \_\_\_\_\_

Means of communication (telephone number,  
fax number, e-mail address) \_\_\_\_\_

To the Instruction to Good Pharmacovigilance Practice (EFT)  
Appendix 2

**On the risk management plan (RMP)  
EXAMINATION VIEW**

No \_\_\_\_\_

Date \_\_\_\_\_

Trade title of the medicinal product \_\_\_\_\_

Active Pharmaceutical Ingredients (s) \_\_\_\_\_

Anatomical-therapeutic-chemical code / ATC code \_\_\_\_\_

Pharmaceutical form \_\_\_\_\_

License holder, country / Marketing Authorization holder, country \_\_\_\_\_

Number of Registration Certificate \_\_\_\_\_

RMP version number \_\_\_\_\_

Data lock point \_\_\_\_\_

Result of Expertise \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_ P.S.  
(position, surname, name of the authorized person) (signature)

**Periodically updated security report (PSUR)  
EXAMINATION OPINION**

No \_\_\_\_\_

Date \_\_\_\_\_

Trade title of the medicinal product \_\_\_\_\_

Active Pharmaceutical Ingredients (s) \_\_\_\_\_

Anatomical-therapeutic-chemical code / ATC code \_\_\_\_\_

Pharmaceutical form \_\_\_\_\_

License holder, country / Marketing Authorization holder, country \_\_\_\_\_

Number of Registration Certificate \_\_\_\_\_

International birth date of the medicinal product

PSUR reporting period / Period covered by PSUR / PBRER \_\_\_\_\_

Result of Expertise \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_ P.S.  
(position, surname, name of the authorized person) (signature)

**On the main file of the pharmacovigilance system (PSMF)  
Expert opinion**

N<sup>o</sup> \_\_\_\_\_

Date \_\_\_\_\_

License holder / Marketing Authorization holder \_\_\_\_\_

Date of PSMF / PSMF date \_\_\_\_\_

PSMF version number / PSMF version number \_\_\_\_\_

Result of Expertise \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_ P.S.  
(position, surname, name of the authorized person) (signature)