

**RULES OF GOOD PHARMACOVIGILANCE PRACTICE (GVP)  
OF EURASIAN ECONOMIC UNION**

1. DEFINITIONS

For the purpose of this Guidelines the definitions are used that mean the following:

**important missing information** – Significant gaps in available knowledge related to certain aspects of the safety of a medicinal product or to particular patient populations administered a medicinal product.

**important identified risk, important potential risk** – An identified risk or potential risk that could have an impact on the risk-benefit balance of a medicinal product or have implications for public health.

**validated signal** – A signal where the signal validation process of evaluating the data supporting the detected that the available documentation is sufficient to presume a new potential causal association or a new aspect of a known association between the use of the suspected medicinal product and the development of an unfavorable consequence and therefore justifies to the need for a complex of further actions to evaluate the signal.

**occupational exposure** – An exposure to a medicinal product as a result a human being to the medicinal product in the course of performance of one's professional or non-professional occupation.

**data lock point** – The date of termination of the termination of data collection to be included in a Periodic Safety Update Report.

**risk minimization activity (risk minimization measure)** – A complex of measures intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicinal product or to reduce its severity should it occur.

**completed clinical trial** – Study for which a final clinical study report has been prepared.

**closed signal** – A signal for which an evaluation was completed during the reporting period of a periodic safety update report preparation.

**abuse of a medicinal products** – Persistent or sporadic, excessive use of a medicinal

product, which is accompanied by unfavourable psychological or psychological effects.

**identified risk** – An untoward consequence of pharmacotherapy for which there is adequate evidence of an association with the medicinal product of interest.

**individual case safety report (ICSR) (adverse (drug) reaction report)** – An information transferred according to the established form and contents of a one or several suspected adverse drug reactions to a medicinal product that occur in a single patient at a specific point of time.

**solicited sources of individual case safety reports** – Organized data collection systems that include clinical trials (studies), registries, post-marketing programs reflecting personalized use of a medicinal product, other patient support and disease monitoring programs, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

**quality of a pharmacovigilance system** – All the characteristics of the pharmacovigilance system, which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.

**clinical trial (study)** – A clinical trial (study) that satisfies at least one of the following conditions:

- the prescription to a subject of clinical trial of a specific therapeutic strategy (intervention) occurs in advance and is not routine clinical practice (that is, stereotyped (one-type) medical diagnostic and treatment procedures, technologies or activities that are performed for a given patient group or this standard of care) in a state - a member of the Eurasian Economic Union, whose research centers participate in this clinical study;
- the decision to prescribe the investigational medicinal product is taken together with the decision to include the subject in the clinical research;
- subjects of clinical study, in addition to procedures of routine clinical practice, perform additional diagnostic or monitoring procedures;

**quality control and assurance** – Monitoring, assessment, assurance of efficacy and compliance with requirements established for the structural elements and processes of a pharmacovigilance system.

**medicinal product** – A product represent or containing a substance or combination of substances designed for treating or preventing disease in human beings or restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action, or to making a diagnosis of a disease and human condition.

**drug, remedy** – A medicinal product available as a specific dosage form, which interacts with the human body.

**pharmacovigilance system master file (PSMF)** – A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized medicinal products.

**development international birth date (DIBD)** – Date of first approval (or authorisation) for conducting an interventional clinical trial in any country in the world.

**international birth date (IBD)** – The date of the first registration (marketing authorization) in any country in the world for any product containing the certain active substance.

**Good Pharmacovigilance Practices (GVP)** – guidelines for the implementation of pharmacovigilance in the Eurasian Economic Union State Members.

**adverse reaction** – An unintentional, unfavorable reaction of the human body associated with the use of a medicinal (investigational) product and involving at least a possible relationship with the use of the suspected medicinal (investigational) product. Adverse reactions can occur when a medicinal product is used in accordance with the approved Summary of Product Characteristic or in accordance with the Prescribing Information or with the violation of them, or as a result of occupational exposure. Cases where a medicinal product is used with the violation of approved Summary of Product Characteristic or approved Prescribing Information include off-label use, overdose, abuse, misuse, and medication error.

**adverse event** – Any unfavourable change in the health status of a patient or clinical study / trial subject administered a medicinal (investigational) product, regardless of the cause-and-effect relationship with its use.

An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**non-interventional studies** – A study that meets the following conditions:

- the medicinal product is prescribed in accordance with the Summary of Product Characteristic of the medicinal product;
- the decision to prescribe a specific treatment to a patient is not accepted in advance according to the study protocol, but routine clinical practice, and the administration of the medicinal product is clearly separated from the decision to include the patient in the study;

No additional diagnostic or control procedures are applied to patients, and epidemiological methods are used to analyze the data obtained. Non-intervention studies are determined by the methodological approach used, and not by scientific goals. Non-intervention studies include database research or revision of medical records, in which all the phenomena

under consideration have been described (in particular, case-control studies, cross-over and cohort studies).

Non-intervention studies also include studies that involve the collection of primary data (in particular, prospective non-interventional studies and registers in which the findings of the routine treatment process are recorded), provided that the above conditions are met. Interviews, surveys, and blood samples can be conducted in this context within the framework of routine clinical practice;

**misuse** - Intentionally and inappropriately use of the medicinal product not in accordance with the authorized Summary of Product Characteristic or the authorized Prescribing Information.

**unexpected adverse reaction** – An adverse reaction whose nature, severity, or outcome disagree with the information contained in the current Summary of Product Characteristic or in the Investigator's Brochure in the event of an unregistered medicinal product.

**newly identified signal** – A signal identified for the first time during the reporting period of a periodic safety update report, specifying further actions for its assessment.

**company core safety information (CCSI)** – An information related to the safety of a medicinal product and contained in the Company Core Data Sheet of the marketing authorization holder, developed by the marketing authorization holder, and claimed by the marketing authorization holder to have been submitted to the competent authorities of Member States of the Eurasian Economic Union countries where the respective medicinal product is marketed, except where this information is modified upon request of the competent authorities of Member States. The CCSI contains reference information, which defines the status of listed and unlisted adverse drug reactions required for compilation of a periodic safety update report for the medicinal product but which does not define expected and unexpected adverse drug reactions required to fulfill the requirements for expedited adverse reaction reporting.

**missing information** – Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

**development safety update report (DSUR)** – A periodic safety update report for a medicinal product undergoing development.

**medication error** – Any unintentional error of the healthcare professional, patient, or consumer in the prescribing, dispensing, dosage, or administration of a medicinal product.

**overdose** – Administration of a quantity of a medicinal product given per one administration or cumulatively during a day, which is above the maximum recommended dose according to the authorized Summary of Product Characteristic. The cumulative effect of overdose should be taken into account as well.

**company core data sheet (CCDS)** – A document developed by the marketing authorization holder, which contains, along with the Company Core Safety Information, materials related to the indications, dosing, pharmacological properties, and other information concerning the medicinal product.

**periodic safety update report (PSUR)** – A report providing an evaluation of the risk - benefit balance of a medicinal product by the marketing authorization holder at certain time points within the post-marketing stage.

**risk management plan** – A detailed description of the risk management system.

**postauthorisation safety study (PASS)** – Any study related to an authorized medicinal product and conducted with the aim to identifying, characterising or quantifying a safety hazard, confirming the safety profile of a medicinal product, or evaluate the effectiveness of risk management measures. A post-marketing safety study may be an interventional clinical trial, or it may have an observational, non-interventional study design.

**potential risk** – An undesirable consequence of pharmacological therapy for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been duly confirmed.

**consumer** – A person who is not a health care professional, such as a patient, lawyer, friend, or relative (parent), child of a patient.

**off-label** – Intentionally used of the medicinal product for a medical purpose not in accordance with the authorized Summary of Product Characteristic or Prescribing Information.

**safety concern** – An important identifiable risk, important potential risk, or important missing information.

**ongoing clinical trial** – A trial in which enrollment of subjects has already commenced, or currently underway, or in which analyses have been completed but no final clinical trial report is available yet.

**risks related to use of a medicinal product** – Risks associated with the quality, safety, or efficacy of a medicinal product with regard to a patient's or public health or resulting in an undesirable environmental impact.

**serious adverse reaction** – An adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or in a congenital anomaly or birth defect, necessitates medical intervention to prevent the development of the aforementioned conditions. Any unintentional suspected transmission of an infectious agent with a medicinal product is considered a serious adverse reaction as well.

**signal** – Information arising from one or multiple sources, which suggests a new

potentially causal association, or a new aspect of a known association, between the effects of a medicinal product and an event or set of related events, which is judged to be of sufficient likelihood to justify verification of the signal. As a general rule, more than a one single report is required to generate a signal, depending on the seriousness of the adverse event and the quality of the information.

**ongoing signal** – A signal that was detected before the reporting period of a periodic safety update report and was still in the process of assessment at the data lock point.

**quality system of a pharmacovigilance system** – The organizational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system including appropriate resource and documentation management and compliance with regulatory requirements.

**risk management system** – A complex of pharmacovigilance-related activities and interventions designed to identify, characterize, prevent, or minimize risks associated with medicinal products, including assessment of the efficacy of these interventions and activities.

**pharmacovigilance system** – A system used by marketing authorization holders of medicinal products and national competent authorities of Member States of the Eurasian Economic Union Member States to fulfil the pharmacovigilance-related tasks and responsibilities, designed with the aim to monitor the safety of medicinal products, detect in a timely manner any change to risk - benefit balance of medicinal products, and develop and adopt measures ensuring a favourable risk - benefit balance of the use of medicinal products.

**risk-benefit balance** – An estimate of the positive therapeutic effects of a medicinal product compared with the risk associated with its use (the concept of risk applies to any risk associated with the quality, safety, or efficacy of a medicinal product with regard to a patient's or public health).

**spontaneous report (spontaneous notification)** – An unsolicited communication by a health care professional, or consumer to a competent authority of the Eurasian Economic Union Member State, marketing authorization holder, or other authorized organization (such as the World Health Organization, Regional Pharmacovigilance Centres, Poison Control Centres) the data, which describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and which does not derive from a clinical study or any other organized data collection scheme.

**reference safety information** – Information included in the Company Core Safety Information of the Marketing Authorization Holder of the medicinal product.

**significant change in indication** – Changes in therapeutic indications that include a change of authorized indication(s) for use of a medicinal product where the new treatment

target population differs significantly from the one for which the medicinal product was previously authorized; inclusion of a new disease area, a new age group (such as pediatric indications), or a move from severe disease to a less severely affected population; a move from second-line to first-line therapy, and other changes considerably affecting the risk - benefit balance of the medicinal product.

**quality requirements** – The characteristics of a quality system that are likely to produce the desired outcome, or quality objectives.

**pharmacovigilance** – Activities undertaken with the aim to detect, evaluate, understand, and prevent undesirable consequences of the use of medicinal products.

**target population (treatment) (treatment population target)** – Patients that may be administered a medicinal product in accordance with the authorized indication(s) and contraindications specified in the current version of the Summary of Product Characteristic.

## **2. REQUIREMENTS TO QUALITY SYSTEM**

### **2.1. Quality System**

2.1.1. A quality system is an integral component of a pharmacovigilance system. A quality system shall cover the organizational structure, scopes of responsibility, procedures, processes and resources of a pharmacovigilance system. A quality system shall include the proper management of resources, control of compliance with regulatory requirements of EAEU member-states (regulatory standards) and records management.

2.1.2. A quality system includes:

- creation of a system structure and the planning of integrated and concerted processes (quality planning);
- fulfillment of tasks and duties of a quality system (quality control);
- control and assessment of the efficiency of work of the structures and processes of the quality system (quality assurance);
- correction and improvement of the structure and processes of the quality system (quality improvement);

2.1.3. The general goals of a quality system in a pharmacovigilance system are:

- fulfillment of regulatory requirements (regulatory standards) and pharmacovigilance duties;
- prevention of the adverse consequences of the use of authorized medicinal drugs;
- provision of the use of medicinal drugs when benefit exceeds risk;
- assistance in the protection of patients and public health.

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

2.2.1. To fulfill the general goals of quality set forth in item 2.1.3 the following principles should be adhered to while developing systems and processes and fulfilling all tasks and duties:

- provision of meeting the requirements of patients, healthcare workers and society in whole in relation to the safety of medicinal drugs;
- provision of the effective management of quality system implementation and staff motivation;
- involvement of all personnel of an organization (enterprise) into the process of supporting the pharmacovigilance system at the level of duties imposed thereon;
- involvement of all personnel of an organization into the permanent process of upgrading the quality of the pharmacovigilance system;



- organization of a resource base and tasks set before a pharmacovigilance system in the form of structures and processes in such a way that to provide an active, in line with the level of risk, constant work in pharmacovigilance;
- all available evidence on the risk-benefit balance of medicinal products should be sought and assessed, and all data which may influence this balance and the use of a medicinal drug should be reviewed and assessed for further decision taking;
- assistance in the development of the effective cooperation between the developers, MAHs, competent authorities of Member States, healthcare institutions, patients, public healthcare workers, scientific organizations and other parties concerned in accordance with the provisions of the current legislation.

### **2.3. Persons responsible for a quality system**

2.3.1. The provision of the work of a pharmacovigilance system in accordance with the requirements to a quality system is the responsibility of all specialists who perform work on the organization of a quality system. It is necessary to provide a systematic approach to implementation and support of a quality system at a proper level. An organization should provide a sufficient number of competent and trained specialists having a proper professional education for fulfilling a required volume of works on pharmacovigilance at a proper level.

2.3.2. The heads of organizations should provide a system approach to the provision of quality. Within the scope of performing functions involving the provision of a system approach the heads of organizations bear responsibility for:

- provision of the documentation of a quality system in accordance with these requirements;
- provision of the proper control and documentation of all changes in a pharmacovigilance system and a pharmacovigilance quality system;
- provision of the possibility of education;
- provision of required resources (including the required rooms, equipment, etc.);
- regular assessment of a pharmacovigilance system work including the integrated quality system with the confirmation of its efficiency. If necessary, the required corrective and preventive measures should be implemented;
- provision of the availability of an effective mechanism for the implementation of relative measures, should a change in the safety profile of the developed/produced medicinal drugs be detected;
- provision of timely detection and adoption, if necessary, of the corrective and preventive measures, if requirements to the quality of a pharmacovigilance system are not met;

- provision of the regular auditing of the system.

## **2.4. Staff training**

2.4.1. The possibility of providing the required quality of pharmacovigilance process execution and the results obtained is directly connected with the availability of the sufficient number of competent, qualified and well-trained personnel.

2.4.2. An organization should develop and fulfill the plan of training specialists in pharmacovigilance. The education should include basic training and further training during the whole period of work in accordance with the fulfilled functions and assigned tasks. The education should be aimed at improving the corresponding professional skills, introduction of scientific achievements into practice and the performed procedures, the provision of the conformity of all specialists to qualification requirements, professional skills, knowledge and understanding of the procedures performed in pharmacovigilance. All specialists should be trained in performing procedures in detecting changes in safety profile of medicinal drugs.

2.4.3. The training processes which an organization applies should include the elements of control of the results of education when the required understanding and fulfillment of pharmacovigilance functions are achieved.

2.4.4. An organization should conduct a relative training in certain aspects of pharmacovigilance for specialists of other departments whose activity may influence the indices of a pharmacovigilance system and the fulfillment of pharmacovigilance functions. This activity includes but not limited to the following types: the conduct of clinical studies/trials, complaints handling, preparation of medical information, sale and marketing, preparation of registration documents, legal issues and audit.

## **2.5. Facilities and equipment for pharmacovigilance**

2.5.1. The achievement of a required level of quality in the performance of pharmacovigilance processes and the received results is also connected with the provision of the system with necessary facilities and equipment used in these processes.

2.5.2. Facilities and equipment should be located, constructed, adapted and maintained in such a way that corresponds to a target goal according to quality aims in pharmacovigilance. Facilities, equipment and their functional properties important for carrying out pharmacovigilance are subject to a relating check, qualification and/or validation to confirm compliance with a target goal. To determine a scope of examination, qualification or validation the documented assessment of risk should be used. This method of risk management should be used during the whole lifetime of facilities and equipment with regard to such factors as

influence on a patient's safety and data quality and the complexity of corresponding facilities and equipment.

## **2.6. Provision of compliance with the legal requirements of the member states, International Treaties and legislation of the Union by MAHs**

2.6.1. For the purpose of providing compliance with regulatory requirements (regulatory standards) MAHs should fulfill special processes for assuring quality of a system the goal of which is:

- execution of constant pharmacovigilance data monitoring, development and implementation of risk minimization measures when determining their necessity, the proper assessment of safety data irrespective of their source (from patients, medical and pharmaceutical workers, those published in medical literature, identified during post-authorization studies);

- execution of the scientific assessment of the whole information on safety profile of a medicinal drug including information on adverse reactions developed as well while using a medicinal drug not in compliance with the approved medicinal product information or instruction for medical use (package leaflet);

- to meet legislative requirements of Member State to submit to a competent authority of Member State information on adverse reactions and other information on safety. For the purpose of the proper fulfillment of this function and provision of quality, integrity and completeness of provided information, the proper validation of signals and the exclusion of message duplication the corresponding standard operating procedures should be developed and implemented;

- provision of an effective interrelation with competent authorities of Member States including information on changes in the safety profile of medicinal drugs and new risks, in a master file of pharmacovigilance system, a risk management system, risk minimization measures, a periodic safety report, corrective and preventive measures, post-authorization safety studies;

- provision of compliance of medicinal product information (instruction for medical use, package leaflet) with current knowledge;

- provision of public healthcare workers and patients with relative safety information.

## **2.7. Assurance of compliance with the legal requirements of the member states, International Treaties and legislation of the Union**

2.7.1. Competent authorities of Member States should have a relative quality assurance

system for processes to provide:

- assessment of quality of provided pharmacovigilance data;
- assessment and processing of pharmacovigilance data in accordance with current legislative requirements;
- ensuring guaranteed independence in performing pharmacovigilance activity;
- effective informing of patients, public healthcare workers, MAHs and society in whole;
- conduct of inspections including pre-authorization inspection.

2.7.2. Independence in performing pharmacovigilance activity is determined by taking all regulatory decisions in the interest of a patient's health and public health.

## **2.8. Records management**

2.8.1. A records management system is a part of a quality system; it covers all documents of pharmacovigilance system and provides the possibility of data search and traceability of performed procedures including procedures for the assessment of new safety data in relation to the time of assessment performance and decisions taken.

2.8.2. A records management system should provide:

- pharmacovigilance data quality including completeness, accuracy and integrity;
- effective internal and external transmission of data;
- retention of documents relating to pharmacovigilance systems and the performance of pharmacovigilance for each medicinal drug according to applicable retention periods.

2.8.3. An Marketing Authorization Holder of the medicinal product (MAH) should provide proper documentation, handling and storage of all information on pharmacovigilance for performing procedures of the accurate reporting, interpretation and verification of data. An MAH should ensure the system of traceability and subsequent assessment of messages of adverse reactions.

Under these Guidelines the “reporting” means a process for submission in accordance with the established procedure the information on adverse drug reactions to competent authorities of Member States or to the expert organizations under the competent authority responsibility which are authorized for pharmacovigilance activities.

2.8.4. A records management system should include a complex of measures for providing safety and confidentiality of data to fulfill personal patient data protection requirements in accordance with the current legislative requirements. The mentioned above measures should include a strict restriction of access to documentation and databases except authorized persons.

2.8.5. A records management system should include the processes of providing pharmacovigilance information protection from loss and destruction.

## **2.9. Quality system documentation**

2.9.1. All elements, requirements and provisions of a quality system should be duly documented and systematized in the form of written manuals and procedures such as a quality plan, quality guidance and quality reports.

2.9.2. A quality plan determines the main goals of a quality system and processes which should be introduced to achieve the target goals. Quality procedures are a description of the established order of performing processes and may have a form of standard operating procedures and other forms of operating instructions or guidance. A quality guidance determines the area of distribution of a quality system, processes of a quality system and their interconnection. Quality reports include the obtained results of the system work or the confirmation of the executed activity.

2.9.3. A quality system should be presented in the following documents:

- documentation on the organizational structure and staff duties;
- an education plan and reports on training given;
- instructions for the compliance management process;
- instructions on pharmacovigilance critical processes including the provision of process continuity;
- process performance indicators which are used for the permanent monitoring of the proper fulfillment of pharmacovigilance functions;
- audit reports and quality system subsequent audit reports including the obtained data and received results.

2.9.4. Quality system documentation should also include:

- methods of monitoring the efficiency of quality system functioning and in particular its ability to fulfill the tasks of a quality system;
- reports on results of performed pharmacovigilance procedures which confirm the fulfillment of all required stages and actions;
- documents and reports on facilities and equipment including the check of functional properties; activity by qualification and validation which confirm the fulfillment of all stages of corresponding requirements, protocols and procedures;
- reports that confirm the control of deviations from the established quality system, the taking of corrective and preventive measures, assessment of the efficiency of the taken measures.

## **2.10. Additional quality system documentation by MAH**

In addition to the documentation required under a quality system an MAH should document an organizational structure which determined a hierarchic relationship between

management personnel and supervisory personnel and the duties and functions of the personnel, a resources management system.

## **2.11. Additional quality system documentation by competent authorities of Member States**

In addition to the documentation required under a quality system a competent authority of Member States should document an organizational structure, the assignments of tasks and responsibilities of all personnel and appoint contact persons to provide interaction between competent authorities of Member States, MAHs and persons who give information on risks connected with medicinal drugs.

## **2.12. Critical processes in pharmacovigilance**

### ***2.12.1. Critical processes in pharmacovigilance include:***

- constant monitoring of the safety profile and risk-benefit balance of authorized medicinal products;
- introduction, implementation and evaluation of the risk management system with the assessment of risk minimization measures;
- procedures of work with individual adverse reaction reports: collection, processing, management, quality control, receipt of missing data, number assignment, qualification, discovering repeated reports, assessment and timely presentation;
- detection, investigation and assessment of signals;
- development, preparation (including the assessment of data and quality control), presentation and assessment of periodic safety reports;
- fulfillment of obligations on summoning by competent authorities of Member States and provision of answers to competent authorities of Member States' requests, including provision of accurate and complete information to competent authorities of Member States;
- provision of interaction between pharmacovigilance and the system of quality control of medicinal drugs;
- provision of information to competent authorities of Member States on all changes in the assessment of the risk-benefit balance of authorized medicinal drugs;
- provision of information to healthcare and pharmaceutical professionals on all changes in the assessment of the risk-benefit balance to ensure safety and efficient use of medicinal drugs;

- provision of medicinal drug information maintenance including instruction for medical use, in accordance with the current level of scientific medical knowledge including conclusions made on the assessment and recommendations of competent authorities of Member States;
- fulfillment of all required actions in case of change in the authorization status because of the revision of safety profile.

**2.12.2. *The process continuity assurance plan should include:***

- determination of events that may significantly influence a company's staff in whole or the structures and processes of pharmacovigilance in particular;
- standby systems in case of necessity of the urgent exchange of information intracompany, with other organizations which distribute the execution of pharmacovigilance functions, with other developers/MAHs and competent authorities of Member States.

**2.13. Control of the functioning and efficiency of the pharmacovigilance system and its quality system**

2.13.1. Methods of control of the functioning and efficiency of the pharmacovigilance system should include:

- overview and analysis of the system by persons responsible for the system management;
- audits;
- compliance control;
- inspections;
- evaluation of the efficiency of the taken risk minimization measures and the provision of safe and effective use of medicinal drugs.

2.13.2. To conduct monitoring in a company there should be first determined indicators by which the assessment of efficiency of a pharmacovigilance system is carried out from the viewpoint of quality requirements.

2.13.3. A quality system audit based on risk assessment should be conducted regularly in a certain period to confirm compliance with established quality requirements and determine efficiency. A quality system audit should include an audit of a pharmacovigilance system having an integrated quality system. An audit should be carried out by specialists not involved into the performance of functions and procedures subject to audit. By the results of each quality system audit and a subsequent audit there should be made a report which is to be evaluated by persons responsible for the organization of corresponding audited processes. If necessary, corrective and preventive measures should be taken by the results of the audit.

2.13.4. Competent authorities of Member States should provide the monitoring of performance by MAHs of their pharmacovigilance functions and obligations established by

legislation. The measures for the provision of monitoring include the inspection of MAHs by competent authorities of Member States.

#### **2.14. A Qualified person responsible for pharmacovigilance**

2.14.1. An MAH should appoint and have at its permanent disposal a qualified person responsible for pharmacovigilance (QPPV) in the member-states. An MAH informs on the qualified person's name and contact details to competent authorities of Member States. When changing this information an MAH should inform competent authorities of Member States in time set by the national legislation.

2.14.2. In each pharmacovigilance system there should be only one QPPV. More than one MAH, in the common or separate systems of pharmacovigilance, may use the qualified person's services or a person may perform the QPPV's functions for more than one pharmacovigilance system of one MAH providing that the QPPV is able to perform all his duties. In addition to the QPPV, the competent bodies of member-states may on legal grounds require the assignment of a contact person for pharmacovigilance at the national level, reporting to the QPPV. A contact person at the national level may also act as the QPPV.

2.14.3. The QPPV duties should be defined in the job description.

2.14.4. An MAH confers the qualified person with sufficient powers for managing a pharmacovigilance activity and a quality system. An MAH gives the QPPV access to the pharmacovigilance system master file and also powers thereunder and provides the receipt of information on any changes in the master file. Powers under a pharmacovigilance system and a master file of the pharmacovigilance system should permit the QPPV to introduce changes into the system, risk management plans and the preparation of regulating actions in response to emergency situations in safety profile change.

2.14.5. An MAH provides the availability of all systems and processes which permit the QPPV to fulfill duties imposed thereon. For this purpose an MAH develops mechanisms whereby the QPPV receives all necessary information and has access to all data which he may need, for example:

- emergency situations in changing safety profile and all other information in relation to the assessment of risk-benefit balance of medicinal drugs which are covered by the pharmacovigilance system;
- the ongoing and completed clinical studies/trials and other studies/trials which an MAH is aware of and which may be related to medicinal drug safety;
- information from other sources, except the sources of an MAH, for example, sources with which an MAH has contractual agreements;



· the pharmacovigilance procedures which an MAH develops at each level to provide consistency and in-house compliance with the requirements.

2.14.6. The QPPV receives information from executive staff by the results of permanent quality system reviews and measures taken; and data on compliance with the requirements, and forthcoming audits of the pharmacovigilance system The QPPV has powers to initiate audit, if necessary. Executive staff will give the QPPV a copy of the plan of corrective and preventive measures after each audit so that the QPPV may assure himself of the corresponding corrective measures being taken.

2.14.7. An MAH will make it possible for the QPPV to receive information from adverse reactions database he has at his disposal.

## **2.15. Qualification of a person authorized for pharmacovigilance in the EAEU**

2.15.1. The QPPV should have corresponding theoretical and practical knowledge on conducting pharmacovigilance activity. The QPPV should have skills in the management of pharmacovigilance systems and conducting expertise or have access to conducting expertise in such spheres as medicine, pharmaceutical sciences and epidemiology and biostatistics.

2.15.2. An MAH will conduct training for the QPPV in the areas of his pharmacovigilance system before the qualified person's taking his post as a qualified person. The training and its results should be duly documented.

## **2.16. Functions of a person qualified for pharmacovigilance in the EAEU**

2.16.1. A person qualified for pharmacovigilance in the EAEU is a physical person.

2.16.2. The QPPV whom the MAH appoints should have a proper qualification (see item 2.15) and be at the MAH's constant disposal. The QPPV shall reside and work in one of the EAEU member-states. The QPPV shall be responsible for the creation and functioning of the MAH's pharmacovigilance system and, consequently, will have sufficient powers to influence the pharmacovigilance activity and the quality system of the pharmacovigilance system, the assistance, compliance and improving the observance of legislative requirements of the EAEU member-states. Consequently, the QPPV shall have powers and responsibility relating to a pharmacovigilance system master file so as to provide and improve the observance of legislative requirements of the EAEU member-states.

2.16.3. As for medicinal drugs that are covered by the pharmacovigilance system of the MAH the QPPV has the following duties:

· to carry on the review of the safety profiles of medicinal drugs and emergency situations in safety profile change;

- to possess full information on the conditions and duties established upon issuing market authorizations and other obligations relating to the safety and safe use of medicinal drugs;
- to possess full information on risk minimization measures;
- to take part in reviewing and approving the protocols of the post-authorization safety studies;
- to possess full information on post-authorization safety studies the conduct of which the competent authority of the member-states has instituted, including the results of such studies;
- to add risk management plans;
- to ensure the fulfillment of pharmacovigilance functions and submit all documents relating to pharmacovigilance according to the legal requirements of the member states, International Treaties and legislation of the Union;
- to provide the required quality including the accuracy and completeness of pharmacovigilance data submitted to the competent authorities of Member States of the EAEU member-states;
- to provide full and timely answers to all requests from competent authorities of Member States to submit additional information necessary to estimate the benefit and risk of medicinal drugs;
- to submit any information concerning the assessment of the risk-benefit balance to competent authorities of Member States in the EAEU member-states;
- to provide assistance in the preparation of regulatory measures in response to safety emergency situations (for example, changes in medicinal use recommendations, urgent restrictions and bringing information to patients and healthcare professions);
- to function as a single pharmacovigilance contact person for competent authorities of Member States of the EAEU member-states and as a contact person for pharmacovigilance inspections with 24-hour access.

2.16.4. The QPPV carries out control of functioning all aspects of the pharmacovigilance system including its quality system (for example, standard operating procedures, contractual agreements, database operations, fulfillment of the quality system requirements, observance of requirements to the presentation of data in the part of completeness and good-timing; submission of periodic safety reports, audit reports and staff training in pharmacovigilance). The QPPV shall possess information on the validation status of database on medicinal drug adverse reactions including all deficiencies detected during validation and corrective actions undertaken. The QPPV shall also possess information on all significant changes entered into database (for example, changes that may influence the activity of pharmacovigilance).

The QPPV may delegate the fulfillment of specific tasks under his surveillance to persons

having relative qualification and training, for example, carrying out activities as safety experts of certain medicinal drugs assuming that the QPPV will conduct control of the functioning of the whole system and safety profiles of all medicinal drugs. Such a delegation of the functions performed should be duly documented.

### **2.17. Specific processes of quality system of the MAHs in the EAEU**

2.17.1. An MAH should develop additional special processes of a quality system with the aim of:

- submitting data on adverse reactions into the national databases of the EAEU member-states within the time required by legislation;
- retention of documents which describe the pharmacovigilance system till the system described in the master file of the pharmacovigilance system exists during at least 5 years after it ceases to exist;
- retention of pharmacovigilance data and documents relating to authorized medicinal drugs within at least 10 years upon termination of certificates of state registration;
- updating information on medicinal drugs according to the latest scientific knowledge including the assessment of the safety profile and risk-benefit balance and also recommendations placed on the web-portals of competent authorities of Member States. For this purpose an MAH constantly checks the web-portals of competent authorities of Member States for corresponding changes in the assessment of the safety profile and risk-benefit balance including changes in recommendations for medicinal use and other measures of a regulatory nature.

2.17.2. Within the period of documentation retention the MAHs provide the recoverability of documents.

2.17.3. Documents may be retained in electronic format providing the proper validation of the electronic system and the existence of agreements on the system protection, access and data backup. In case of converting documents from paper format into electronic one the process of conversion should guarantee the preservation of all information in the readable format and ensure the preservation of readability for the whole period of storage by means used for storage.

2.17.4. Should the MAH's business be taken over, all documents shall be handed over and retained in full volume.

### **2.18. Requirements to the quality system when an MAH delegates the performed pharmacovigilance functions**

2.18.1. An MAH may delegates all or part of his pharmacovigilance tasks including a

QPPV's functions to another organization or person (if to such a person may be applied the requirements same as to an organization). Given that the absolute responsibility for fulfilling pharmacovigilance tasks and responsibilities, provision of quality and integrity of the pharmacovigilance system will always bear the MAH.

2.18.2. In case of delegating specified pharmacovigilance tasks by a MAH to another organization, the MAH reserves the responsibility for using an effective quality system for executing these tasks. Requirements to the pharmacovigilance system determined by a good pharmacovigilance practice are also applied to the other organization which the tasks were delegated to.

2.18.3. When delegating tasks to another organization an MAH will provide a detailed accurate and regular updated documentation of contractual agreements between the MAH and another organization with the description of agreements on delegated tasks and responsibility of each of the parties. The description of a delegated activity and/or services should be included in the master file of the pharmacovigilance system. Another organization may be inspected at the discretion of a competent authority in a relative EAEU member-state.

2.18.4. To control the execution of contractual pharmacovigilance agreements it is recommended that the MAH should regular audit the organizations which were delegated pharmacovigilance functions.

## **2.19. General pharmacovigilance duties in the frame of the legal requirements of the member states, International Treaties and legislation of the Union**

2.19.1 The competent authorities of Member States of the EAEU member-states shall bear responsibility for fulfilling the pharmacovigilance tasks which are assigned to them by the corresponding national legislation. For this purpose each competent authority of an EAEU member-state provides the functioning of the pharmacovigilance system, and creates and applies an appropriate efficient quality system of the conducted pharmacovigilance activity.

2.19.2. The EAEU member-states will cooperate to constantly improve the pharmacovigilance systems for achieving high standards of public health protection including the use of united resources to optimize the use of the available resource base within the EAEU.

2.19.3. The member-states shall determine contact points to streamline the interaction of the competent authorities of Member States, MAHs and persons who provide information on pharmacovigilance.

## **2.20. Functions of the competent authorities of Member States**

2.20.1. Each member-state shall appoint a competent authority responsible for

performing pharmacovigilance.

2.20.2. Each competent authority of an member-state shall introduce and provide effective functioning of a pharmacovigilance system when it performs its tasks and participates in pharmacovigilance activity in the EAEU. In this context competent authority of an EAEU member-state will be responsible for safety control of each medicinal drug registered within the EAEU member-state.

2.20.3. The tasks and duties of pharmacovigilance competent authorities of Member States include cooperation when signals are detected and the introduction of risk minimization measures when corresponding decisions are taken.

2.20.4. The competent authorities of Member States will be responsible for verifying the performance of medicinal drug pharmacovigilance by MAHs on their territories including the inspections of the MAHs' pharmacovigilance systems. The competent authority of each EAEU member-state will provide the presentation of all data on each pharmacovigilance procedure to the competent authorities of Member States in accordance with the current legislation and the regulatory requirements of the EAEU member-states.

## **2.21. Planning of readiness to pharmacovigilance under emergency situations in public healthcare**

2.21.1. The pharmacovigilance systems of the MAHs and competent authorities of Member States shall be adapted to emergency situations in public healthcare. Necessary plans of readiness shall be developed when needed.

An emergency situation in public healthcare is a threat to public health acknowledged by the World Health Organization (WHO) or by the authorized bodies of the EAEU member-states.

Pharmacovigilance requirements to emergency situations in public healthcare are estimated by the competent authorities of Member States on an individual basis. MAHs and general public are informed on pharmacovigilance requirements. Competent authorities of Member States publish notifications of emergency situations on their web-sites.

### **3. PHARMACOVIGILANCE SYSTEM MASTER FILE**

#### **3.1. Structures and processes**

3.1.1. A master file of a pharmacovigilance system is designed for describing a pharmacovigilance system and documentary confirmation of its compliance with regulatory requirements of EAEU member-states. The master file permits to appropriately carry out the planning and auditing of a pharmacovigilance system by an MAH and also inspections by competent authorities of Member States. The master file includes review of an MAH's pharmacovigilance system which permits to make its general assessment by competent authorities of Member States at the authorization and post-authorization stages.

3.1.2. The making of a master file and information support therein at an actual level will permit the MAH and the QPPV:

- to make sure that the pharmacovigilance system has been introduced according to legislative requirements of EAEU member-states;
- to confirm the system compliance with current requirements;
- to obtain information on the system inefficiency or to detect incompliance with the current requirements;
- to obtain information on risks or the inefficiency of the performance of certain directions of pharmacovigilance activity.

3.1.3. The use of master-file promotes the optimization of the process of appropriate system management and the improvement of a pharmacovigilance system. Requirements to the submission of a brief description of an MAH's pharmacovigilance system in the form of a master file and the chronology of change introductions by a corresponding authority facilitate the planning and effective inspecting by competent authorities of Member States on the basis of a method of risk assessment.

#### **3.2. Registration and maintenance of a master-file**

##### **3.2.1. Location**

A master file of a pharmacovigilance system shall be located within the EAEU or at the place of principal activity in a pharmacovigilance system or at the place where a QPPV bears responsibility for conducting pharmacovigilance, irrespective of the format (paper or electronic). The competent authority of an EAEU member-state shall be informed on of the place of location of a master file and shall be immediately informed on any changes in its location. The required information on the location of a master file includes the indication of the physical address of an MAH or a third party under contract. This address may differ from the

address of an applicant/MAH, for example, the address of another office of the MAH, or in case of the performance of principal activity by a third party under contract. When determining the place of principal pharmacovigilance activity an MAH shall take into consideration the most relevant place of location of a pharmacovigilance system as a whole. An MAH should have a relative justification of decision taking on the location of a master file. In a situation when the principal activity is carried out outside the EAEU or it is impossible to determine the main place location, the place of location of a master file will be at default a QPPV's place of activity.

### ***3.2.2. The delegation of powers for a master file of a pharmacovigilance system***

3.2.2.1. The transfer or delegation of duties and activity for a master file of a pharmacovigilance system should be documented and controlled to confirm that the MAH performs his duties. A QPPV should be informed on changes introduced into a master file of pharmacovigilance system for his exercising powers to introduce changes for improving the system. The types of changes which a QPPV should be immediately informed on:

- changes in a master file of a pharmacovigilance system or in its location which competent authorities of Member States should be informed on;

- addition of corrective and/or preventive measures into a master file of a pharmacovigilance system (for example, by the results of audits and inspections) and management of deviations from the processes specified in the quality management system of a pharmacovigilance system;

- changes in information entered in a master file which meet the criteria of the appropriate control of a pharmacovigilance system (in the framework of the capacity of the system, functioning and observance of requirements);

- changes in the established agreement on the submission of a master file of a pharmacovigilance system to competent authorities of Member States;

3.2.2.2. A qualified person for pharmacovigilance should confirm in writing that he was informed on the following changes:

- inclusion of medicinal drugs into the pharmacovigilance system which the QPPV is responsible for;

- delegation of pharmacovigilance system duties to the QPPV.

### **3.3. Description of pharmacovigilance systems**

A master file of a pharmacovigilance system should describe a pharmacovigilance system of 1 or more medicinal drugs of an MAH. Different pharmacovigilance systems may be applied to different categories of medicinal drugs of an MAH. Each such a system should be described in a separate master file of a pharmacovigilance system. These master files should in whole

cover all an MAH's medicinal drugs which were issued a state market authorization certificate.

If an MAH functions more than 1 pharmacovigilance system, for example, specific pharmacovigilance systems to determine the types of medicinal drugs (vaccines, sanitary and hygienic products, etc.) or a pharmacovigilance system covers medicinal drugs of more than 1 MAH, then 1 master file of the pharmacovigilance system is presented which describes each system.

A qualified person for pharmacovigilance responsible for the creation and maintenance of a pharmacovigilance system described in a master file of a pharmacovigilance system should be appointed by an MAH.

If one pharmacovigilance system is used by several MAHs, each MAH bears responsibility for the availability of a master file of the pharmacovigilance system which describes a pharmacovigilance system for the products he turns out. An MAH may delegate through a written agreement (for example, to a license partner or a subcontractor) a part or all pharmacovigilance activity, for proper fulfillment of which the MAH will bear responsibility. In this case the master file of the MAH's pharmacovigilance system may have a cross reference to all or part of the master file of the pharmacovigilance system which is under control of the system of the party which was delegated the activity based on the agreement on access to this system information on the part of the MAH and competent authorities of Member States. The MAH should provide the compliance of the content of the reference file to the pharmacovigilance system applied to a medicinal drug(s).

In appropriate cases the attachment specifies the list of all master files of the pharmacovigilance system supported by one MAH. The attached information includes data on the location of master files, information on the QPPV and a corresponding medicinal drug(s).

The brief information submitted to competent authorities of Member States should not include several locations of one master file of the pharmacovigilance system.

On delegating the pharmacovigilance activity and its master file an MAH reserves all full responsibility for the pharmacovigilance system, submission of information on the location of the pharmacovigilance system master file, maintaining the pharmacovigilance system master file and its submission to competent authorities of Member States on request. There should be written agreements with the description of functions and responsibilities for the pharmacovigilance system master file, for its submission and maintenance, and for the conduct of pharmacovigilance.

If several MAHs use a pharmacovigilance system it is recommended that the partners should agree upon a joint maintenance of the corresponding sections within their own master files in the system. The accessibility of a pharmacovigilance system master file for all



corresponding MAHs and its submission to competent authorities of Member States should be specified in written agreements. It is important that an MAH will assure itself that the pharmacovigilance system covering its products meets all necessary requirements.

### **3.4. Mandatory information in a pharmacovigilance system master file**

A pharmacovigilance system master file should include appropriate documents with the description of a pharmacovigilance system. The content of a pharmacovigilance system master file should reflect the accessibility of information on the safety of medicinal drugs authorized in the EAEU member-states. The content should have index to provide the possibility of quick familiarization in the document.

#### ***3.4.1. The master file section of a QPPV.***

Information on a QPPV in a master file should include:

- description of obligations which guaranty that a QPPV has corresponding pharmacovigilance system powers to provide, promote and increase the level of compliance with the requirements.
- a brief summary with key information on the role of a QPPV;
- contact information of a QPPV, which should include the name, postal address, telephone number, fax, e-mail and business address;
- information on the use of standby agreements, if a qualified person responsible for pharmacovigilance is absent. If a QPPV delegates certain tasks to another executor, the list of the delegated tasks should be included into the attachment with specification of the description of the delegated activity and whom it was delegated to;
- description of the qualification of the QPPV and the experience relating to pharmacovigilance activity;

#### ***3.4.2. The master file section of the organizational structure of an MAH***

3.4.2.1. It is necessary to submit the description of the organizational structure of the appropriate pharmacovigilance system of an MAH. The description should give a clear-cut idea of involved companies, main departments of pharmacovigilance and the interrelations between the organizations and structural units having relations to the performance of pharmacovigilance activity. A pharmacovigilance system master file should include the following information:

- the organization structure of an MAH, including the designation of the QPPV's position in the organization.
- the site address at which pharmacovigilance activity is carried out including the collection and assessment of individual reports on adverse reactions, the data entry of the reports into the safety database, the preparation of a periodical safety update report, the

identification and analysis of signals, the maintenance of risk management plans, the management of pre- and post-authorization studies/trials and management of changes introduced in medicinal drug safety information.

#### 3.4.2.2. The master file section on outsourced activity.

3.4.2.2.1. A pharmacovigilance system master file should contain the description of the delegated activity and/or services for the fulfillment of pharmacovigilance obligations.

3.4.2.2.2. Information in the section should include the confirmation of interconnection with other organizational structures (e.g. joint marketing agreements, pharmacovigilance agreements with a partner, and other commercial contracts).. The description of the site and structure of the outsourced contracts and agreements on the fulfillment of pharmacovigilance activity should be given. Such a description may be in the form of a list/table: participating parties, undertaken obligations, an appropriate medicinal drug(s) and territories of member states where the pharmacovigilance activity is carried out. In case of listing agreements, this list should be structured with the types of organizations which provide services (for example, medical information, audits, patient support programs,, study data processing), with the types of commercial agreements (product distribution agreement, joint marketing, licensing in product registration etc.) and with the types of technical providers (computer systems hosting, archiving and storage of pharmacovigilance information etc.). Individual contractual agreements are submitted by request from national competent bodies or during inspection and audit, their list is given in the attachments.

3.4.2.2.3. A pharmacovigilance system master file shall contain copies of signed agreements on delegating significant activity, such as:

- providing services on pharmacovigilance (a pharmacovigilance qualified person, safety data entry, preparation of a periodic safety update report, submission of individual case safety reports on adverse reactions in electronic format, safety data assessment, etc.);
- Delegation of activity for a pharmacovigilance system master file.

#### **3.4.3. The master file section on safety data sources**

3.4.3.1. The description of the main safety units for the collection of adverse reaction individual reports should include all in a global sense parties responsible for collection of reports received on request and spontaneous reports of adverse reactions to medicinal drugs authorized within the member-states. Hereinto should be included the sites of medical information and affiliated offices. Such information may be in the form of a list with specification of a country, nature of activity and medicinal drugs (if such activity depends on the type of a medicinal drug). Information on third parties (license partners or local distributing/marketing agreements) also should be included into the section where contracts and

agreements are described.

3.4.3.2. Safety information sources should also include the current list of studies/trials, registers, programs of support or observations sponsored by an MAH. The list should describe at the world level a status of each study/program, appropriate countries, medicinal drugs and main goals. Interventional and non-interventional studies/trials should be specified separately according to the active substance of medicinal drugs. The list should contain all studies/programs, current studies/programs and also the studies/programs completed within the last two years.

#### ***3.4.4. The master file section on computer systems and databases***

3.4.4.1. A pharmacovigilance system master file should describe the location, functional capabilities and operating responsibility for computer systems and databases used for obtaining, verification, presentation of safety information and the assessment of its consistency with the assigned tasks.

3.4.4.2. If a number of computer systems/databases is used, their applicability to the pharmacovigilance activity should be described in such a way that the volume of computerization was understandable within the pharmacovigilance system. The status of validation of the main aspects of the functional capacities of a computer system should also be described as well as the change of control, the structure of tests, standby procedures and archives of electronic data important for meeting the pharmacovigilance requirements, the description of the available documentation. As for paper systems (when the electronic system is used only for the expedite reporting of ICSR), it is necessary to describe data management, mechanisms used to provide integrity and access to data.

#### ***3.4.5. The master file section on processes***

3.4.5.1. An important component of any pharmacovigilance system is the availability of written standard procedures at the place of activity. Sections 2.6, 2.9-2.12 of the guidance describes the required minimal set of the pharmacovigilance written procedures. A pharmacovigilance system master file should describe the available procedure documentation (references to concrete standard operating procedures, guidances, etc.), types of data (for example, the type of data on individual adverse reaction cases) and the method of record keeping (for example, safety database, and paper files at the place of receipt).

3.4.5.2. A pharmacovigilance system master file should include the description of processes, procedures for the processing and registration of data, while performing pharmacovigilance activity, which should include the following aspects:

- permanent monitoring of the risk-benefit profile of a medicinal drug, the results of an assessment and the decision making process for taking appropriate measures; the process of

signal generation, verification and evaluation; receipt of output data form safety databases, data exchange with clinic departments, etc.;

- risk management system and monitoring of the outcome of risk minimization measures; if this process involves several departments, the order of their interaction is determined by written procedures or agreements;

- ICSR collection, verification, follow up, assessment and reporting; procedures in this section should clarify what are local and what are global activities. ;

- the scheduling , making and submission of periodic safety update reports;

- communication of safety concerns to consumers, healthcare professionals and competent authorities of Member States;

- implementation of safety variations to the summary of product characteristics and patient information leaflet; the procedures should cover both internal and external communications.

3.4.5.3. For each line of activity an MAH should be able to present the confirmation of the functioning of the system of timely proper decision and action taking.

3.4.5.4. There should be presented data on the functioning of other directions of activity confirming the availability of a proper system of quality assurance in the pharmacovigilance system. In particular this includes a QPPV's functions and duties, responses to competent authorities of Member States' requests for information, literature search, and the control of changes in safety databases, agreements on safety data exchange, archiving of safety data, pharmacovigilance auditing, quality system control and training. During the review a table with all pharmacovigilance procedure documents (the name and number) may be used.

#### ***3.4.6. The master file section on a pharmacovigilance system performance***

A pharmacovigilance system master file should include the confirmation of the permanent monitoring of the pharmacovigilance system functioning, including the control of the basic results. A pharmacovigilance system master file should include the description of the monitoring methods and contain at least:

- description of a procedure for estimating the correctness of submitting individual adverse reaction reports. There should be submitted the pictures/diagrams that confirm the timeliness of the presentation of information in accordance with the requirements of the current legislation of EAEU member-states;

- the description of control indicators used for quality control of the submitted information and pharmacovigilance activity. It includes information received from competent authorities of Member States relating to the quality of presentation of adverse reaction reports, PSUR or other submitted data;

- the analysis of timeliness of the PSUR submission to the EAEU competent authorities of Member States (it should include the latest data which an MAH uses for assessing the compliance with the requirements);

- the analysis of timeliness of introducing changes in safety against the established deadlines and also the date and description of necessary changes in safety which were identified, but not submitted yet.

- in corresponding cases the analysis of the fulfillment of obligations under the risk management plan or other obligations or requirements relating to pharmacovigilance.

It is necessary to describe and explain the purposes of using a pharmacovigilance system. The attachment to the pharmacovigilance system master file should include a list of activity indices.

In corresponding cases a list of pharmacovigilance activity indices should be included.

#### ***3.4.7. The pharmacovigilance system master file section on quality system***

The section presents the description of the quality management system in the framework of the structure of an organization and the use of the quality system in pharmacovigilance. It includes the following:

##### *3.4.7.1. Procedural documents*

A list of documented procedures and processes which are related to pharmacovigilance activity with the specification of their interrelation with other functions and approaches to the assessment of the procedures. The list shall contain the number of a document, the name, the effective date (for all standard operating procedures, work instructions, manuals, etc.) and the description of access to documents. There should be specified standard operating procedures pertaining to service providers and other third parties.

##### *3.4.7.2. Training*

There is given the description of resource management in the process of performing pharmacovigilance activity:

- the organizational structure with a quantity of people taking part in pharmacovigilance activity, including a reference to the location of qualification documents;

- a list of personnel's locations;

- a short description of the context of training, including a reference to the location of training documents; and

- critical process instructions.

- the personnel shall be appropriately trained in pharmacovigilance activity. This concerns not only to personnel in pharmacovigilance departments, but also persons who may receive safety reports.

### *3.4.7.3. Audit*

Information on the audit of the quality assurance system in the pharmacovigilance system should be included into the pharmacovigilance system master file. The attachment should include the description of the planning method of pharmacovigilance system audits and mechanisms of reporting and the current list of the planned and accomplished audits of the pharmacovigilance system. This list should include the date, area of conduct and the status of audit completion by service providers, the specific types of pharmacovigilance activity or the places of pharmacovigilance functions, and the operating areas of interaction relating to the fulfillment of obligations.

A pharmacovigilance system master file should also include comments on audits during which significant results were received. This means that the results which were estimated as significant or critical ones should be present in the list of accomplished audits; the same concerns a brief description of the corrective or preventive action plan with final schedule times. There should be given a reference to the full report on the accomplished audit, documents with the corrective or preventive action plan. Comments, corrective and preventive measures and notation on the location of the accomplished audit report should be included into a pharmacovigilance system master file until the corrective and/or preventive measures are executed in full scale, i.e. comments will be deleted only when the achieved results of corrective actions are demonstrated and/or confirmation is given or an independent party confirms a significant improvement in the system.

As a means of pharmacovigilance system management and a support tool for making an audit or an inspection a pharmacovigilance system master file should also contain the description of the process of the registration, processing and elimination of deviations revealed in the quality management system.

### *3.4.8. Annex to the master file*

The annex to the pharmacovigilance system master file should include the following documents:

- a list of medicinal drugs which an MAH authorized in the EAEU member-states and other countries, which are covered by the pharmacovigilance system master file, including the name of a medicinal drug, the international nonproprietary name (INN) of the active substance and the name of the country where the certificate of the state registration is valid, the number(s) of the state registration certificates.

- the list should be structured by active substances and in the corresponding cases it is necessary to point out the existence of specific requirements to the drug safety control (for

example, the introduction of risk minimization measures described in the risk management plan).

- in case of joint pharmacovigilance systems there should be included a list of medicinal drugs and MAHs that use the pharmacovigilance system described in the pharmacovigilance system master file, in such a way that a full list of medicinal drugs which the pharmacovigilance system master file covers is available.

- a list of contractual agreements concerning the activity delegated under pharmacovigilance including the corresponding medicinal drugs and the territory(-ies).

- a list of tasks delegated by a qualified person for pharmacovigilance;

- a list of all audits accomplished for 10-year period, and a list of planned audits.

- a list of indicators of pharmacovigilance activities, if applicable.

- a list of other pharmacovigilance system master files under the supervision of an MAH, if applicable.

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

3.5.1. Competent authorities of Member States may ask for information on important changes in the pharmacovigilance system which may include but not limited to the following:

- a) changes in database on the pharmacovigilance system safety which may include changes in the database itself or in interconnected databases, changes in the validation status of the database and changes in information on transmitted or carry-over data;
- b) changes in the rendering significant pharmacovigilance services, especially, if the question is about important contractual agreements on the provision of safety data;
- c) organizational changes, such as a company takeover by another company, merging, change of the place of the pharmacovigilance activity or delegating/transfer of control over the pharmacovigilance system master file.

3.5.2. As the pharmacovigilance system master file includes the lists of medicinal drugs and the types of activity which may periodically be changed, MAHs shall use change control systems and develop the valid methods of permanent awareness of relative changes for the purpose of proper review of the pharmacovigilance system master file. Besides the changes introduced into the pharmacovigilance system master file shall be registered in such a way that the history of changes (with specification of the date and context of changes) was permanently available. The permanently renewed information such as the lists of medicinal drugs and standard operating procedures or compliance data may be registered through the history of changes which may include the controlled system data (e.g., the electronic systems of data management or regulatory and legal databases). Thus, it is possible to manage the changed

versions of documents outside the text content of the pharmacovigilance system master file providing the history of changes accounting and their submission to competent authorities of Member States on request. The significant or important descriptive changes in the text content of the master file may require the creation of a new version of the pharmacovigilance system master file.

3.5.3. MAHs shall justify the chosen method and develop the procedures for documentation control to proper control the process of support of the pharmacovigilance system master file. The basic principle consists in that being a reason for audits and inspections the pharmacovigilance system master file contains the description of the pharmacovigilance system at the current time, but the estimation of the functioning and orientation of the pharmacovigilance system at the previous stages may require the additional familiarization with the system.

3.5.4. When introducing changes into the pharmacovigilance system master file it is also necessary to take into consideration the joint pharmacovigilance systems and the activity delegated under pharmacovigilance. The proper control of changes includes the registration of the date and context of the notifications of competent authorities of Member States, the QPPV and third parties about the introduced changes.

3.5.5. A pharmacovigilance system master file should be in a readable and accessible form. It is necessary to present a description of the procedure of archiving on the electronic and/or printed media of the pharmacovigilance systems master file.

### **3.6. Presentation of a pharmacovigilance system master file**

The QPPV shall have a permanent access to the pharmacovigilance system master file. Competent authorities of Member States shall be provided with a permanent access to the pharmacovigilance system master file on request. Information in the pharmacovigilance system master file should be exhaustive, true and reflect the current pharmacovigilance system at the current time which means the mandatory update of the master file information and, if necessary, the review with regard to the obtained experience, technical and scientific progress and amendments to regulatory requirements (regulatory standards). MAHs should provide competent authorities of Member States with access to the pharmacovigilance system master file for not more than 7 days upon receipt of a corresponding request.

#### ***3.6.1. Format and structure***

The pharmacovigilance system master file may be in electronic format on condition of providing a clear structured printed copy on request by competent authorities of Member States. In any format the pharmacovigilance system master file shall be in readable, full and accessible



form ensuring the possibility of the assessment of all documents and traceability of changes. It may be required to limit access to the pharmacovigilance system master file to provide an appropriate control of its content and the distribution of certain duties on the management of the pharmacovigilance system master file (in the context of the control of changes and archiving).

### **3.7. Pharmacovigilance system stakeholders responsibilities**

#### ***3.7.1. Marketing Authorization Holders***

3.7.1.1. Marketing Authorization Holders should develop and introduce a pharmacovigilance system for control and observation over one or several medicinal drugs. They will be also responsible for the creation and support of the pharmacovigilance system master file which will make registration of the pharmacovigilance activity in relation to one or more authorized medicinal drugs. An MAH should appoint one qualified person for pharmacovigilance who will be responsible for the creation and functioning of the pharmacovigilance system described in the pharmacovigilance system master file.

3.7.1.2. When submitting an application for state registration the applicant shall have at its disposal the description of the pharmacovigilance system which will function on the territory of the state registration of a medicinal drug. In the process of evaluating an application for obtaining permission for state registration the applicant may be asked to submit a copy of the pharmacovigilance system master file for information.

3.7.1.3. An MAH will be responsible for the creation of the pharmacovigilance system master file in the member-states and for registration of the location of the master file in competent authorities of Member States on submitting an application for state registration. In the pharmacovigilance system master file it is necessary to describe the pharmacovigilance system which is valid as of the current date on the territory of the application submission. There may be included information on the system components which will be introduced in future, but they should be specified as the planned ones, but not as the implemented or current ones.

3.7.1.4. The work on the creation, support and presentation of the pharmacovigilance system master file to competent bodies may be assigned to a third party, but an MAH will reserve the full responsibility for compliance with legislative requirements of EAEU member-states. The maintenance of the pharmacovigilance system master file in the current and accessible condition (the permanent access for audit and inspection) may be delegated, an MAH's responsibility for ensuring the performing this function at a level required by EAEU legislation is retained on a permanent basis.

3.7.1.5. In the event of the change of a QPPV or relative contact information and the location of the pharmacovigilance system master file the MAH, the MAH will submit an

application for the corresponding changes to the national competent authorities of Member States. MAHs will also bear responsibility for updating information on a QPPV and the address of location of the pharmacovigilance system master file.

### ***3.7.2. Competent authorities of Member States***

3.7.2.1. Competent authorities of Member States are responsible for monitoring MAHs' pharmacovigilance systems. A full pharmacovigilance system master file may be requested at any time, e.g. in the case of questions on the pharmacovigilance system and/or the safety profile of a medicinal drug or during the preparation to an inspection. Information on changes in the brief information on the pharmacovigilance system or in the content of the pharmacovigilance system master file is also used while planning and conducting the inspection.

3.7.2.2. Competent authorities of Member States will exchange information on pharmacovigilance systems and use the information for convey information to national inspection programs based on risk assessment. The inspectors of the national competent authorities of Member States will inform on the non-compliance with the mandatory regulatory requirements, including incompliance with the requirements for the pharmacovigilance system master file and the pharmacovigilance system.

## **3.8. Accessibility of a pharmacovigilance system master file**

3.8.1. The pharmacovigilance system master file should be maintained in a current state and be permanently available to the QPPV. It should be also permanently accessible for inspection irrespective of the fact whether the notification was sent in advance or was not sent at all.

3.8.2. An MAH should maintain and make available on request from the competent authorities of Member States of the EAEU member-states a copy of the pharmacovigilance system master file. An MAH should submit a copy of the pharmacovigilance system master file not later than 7 days for the date of receipt of the request from the national competent authority. A pharmacovigilance system master file should be presented in a readable electronic format or in a clearly structured printed copy.

3.8.3. If the same pharmacovigilance system master file is used by more than one MAH (where a common pharmacovigilance system is used), the corresponding pharmacovigilance system master file should be accessible to each of them in such a way that each MAH had the possibility to submit a master file to competent authorities of Member States within not more than 7 days upon receipt of request.

3.8.4. The pharmacovigilance system master file is not routinely requested during the assessment of new marketing authorization applications (i.e. before the authorization of a

medicinal drug), but it may be requested for in special cases, in particular, in the event of implementation of a new pharmacovigilance system, or if product specific safety concerns or issues with compliance with the pharmacovigilance regulatory requirements of the EAEU member-states (regulatory standards) have been identified.

## **4. INSPECTION OF THE PHARMACOVIGILANCE SYSTEM**

### **4.1 Introduction**

4.1.1 In order to determine that marketing authorization holders comply with pharmacovigilance obligations and fulfil their pharmacovigilance obligations, the competent authorities of Member States of the Eurasian Economic Union member states concerned shall conduct pharmacovigilance inspections of marketing authorization holders or any organizations employed to fulfil a marketing authorization holder's pharmacovigilance obligations. Pharmacovigilance inspections shall be carried out by inspectors appointed by the national competent authorities of Member States and empowered to inspect the premises, records, materials, documents, and the Pharmacovigilance System Master File of the marketing authorization holder or any organizations employed by the marketing authorization holder to perform pharmacovigilance obligations. Marketing authorization holders are required to provide, upon request of the competent authority, the Pharmacovigilance System Master File, which will be used to inform inspection conduct.

4.1.2 The objectives of pharmacovigilance inspections are

- a) to determine that the marketing authorization holder has personnel, systems, facilities, means and equipment in place to meet their pharmacovigilance obligations;
- b) to identify, evaluate, record, and inform the inspected party of non-compliance which may pose a risk to public health;
- c) to use the inspection results as a basis for actions to be taken by the Marketing Authorization Holder, if necessary.

4.1.3 The competent authority has a right to conduct pre-authorization pharmacovigilance inspections to verify that the pharmacovigilance system currently operated by the Marketing Authorization Holder is consistent with requirements set forth in applicable laws and the Good Pharmacovigilance Practices. Competent authorities of Member States shall interact in exchanging information concerning inspections that are planned and those that have been conducted.

4.1.4 Pharmacovigilance inspection programmes include routine inspections scheduled according to a risk - based approach, and also incorporate "for cause" inspections, which have been triggered to examine suspected non-compliance or potential risks, with an possible impact on the pharmacovigilance functions with regard to a specific medicinal product.

4.1.5 The results of an inspection will be provided to the inspected entity, who will be given the opportunity to comment on any identified non-compliance of the requirements of legislation and good pharmacovigilance practice. Any non-compliance should also be rectified

by the marketing authorization holder in a timely manner through the development and implementation of a corrective and preventive action plan.

4.1.6 If the outcome of the inspection is that the marketing authorization holder does not comply with the pharmacovigilance obligations, competent authority of the member state concerned shall inform the other competent authorities of Eurasian Economic Union member states about the violations identified. Where appropriate, the competent authority of member state concerned shall take the necessary measures to ensure that the marketing authorization holder is subject to effective, proportionate and dissuasive penalties. Information on the conduct and outcome of pharmacovigilance inspections and the follow-up and evaluation of the consequences is made publicly available by the Eurasian Economic Union member states on the websites of the competent authorities of Member States concerned.

## **4.2. Structures and processes**

### ***4.2.1. Inspection types***

#### *4.2.1.1. Overall inspections of the pharmacovigilance system and product-related inspections*

4.2.1.1.1. Pharmacovigilance system inspections are designed to review and analyse the procedures, systems, personnel, facilities, and equipment in place, as well as to determine their compliance with regulatory pharmacovigilance obligations and Good Pharmacovigilance Practice. As part of this review, product specific examples may be used to demonstrate and check the operation of the pharmacovigilance system.

4.2.1.1.2. Product-related pharmacovigilance inspections are focused on assessment and analysis of product-related pharmacovigilance issues. Some aspects of the general pharmacovigilance system used for the functions of the inspected medicinal product may still be examined as part of a product-related inspection.

#### *4.2.1.2. Routine and “for cause” pharmacovigilance inspections*

4.2.1.2.1. Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes. To optimize the planning of pharmacovigilance system monitoring measures, it is recommended that an approach should be implemented that is based on assessment of potential risks to the implementation of respective pharmacovigilance obligations. Scheduled inspections are usually system inspections but one or more specific medicinal products may be selected as examples to verify the implementation of the pharmacovigilance system and to provide practical evidence of its effective functioning and compliance with legal requirements of the member states, International Treaties and legislation of the Union. A standard inspection programme may include, for instance, an assessment of the

system's on particular concerns raised by experts.

4.2.1.2.2. "For cause" pharmacovigilance inspections are undertaken when a triggering factor (systemic problem) is recognized, and an inspection is considered an appropriate way to investigate and evaluate the identified problem. "For cause" inspections focus on specific pharmacovigilance processes or include an examination of identified compliance problems (issues) and their impact for a specific product. In certain cases, full pharmacovigilance system inspections may also be performed resulting from a trigger. "For cause" inspections may arise when one or more of the triggers listed below are identified:

4.2.1.2.2.1. With regard to the risk - benefit balance of the product:

- change in the risk - benefit balance where further examination through an inspection of the pharmacovigilance system is considered appropriate;

- delays or failure to identify or communicate a risk or a change in the risk - benefit balance, or inappropriate performance of this procedure;

- communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the competent authorities of Member States;

- non-compliance with the legal requirements of the member states, International Treaties and legislation of the Union or product safety issues identified during the monitoring of pharmacovigilance activities by the competent authorities of Member States;

- suspension or medicinal product withdrawal with no advance notice to the competent authorities of Member States;

4.2.1.2.2.2. Reporting obligations (expedited and periodic):

- delays or omissions in reporting safety issues in accordance with the legal requirements of the member states, International Treaties and legislation of the Union;

- poor quality (including inaccuracy, untraceability, lack of integrity) or incomplete reports;

- inconsistencies between reports and other information sources;

4.2.1.2.2.3. Requests from the competent authorities of Member States:

- failure to provide the requested information or data within the deadline specified by the competent authorities of Member States;

- poor quality or inadequate provision of data to fulfil requests for information from the competent authorities of Member States;

4.2.1.2.2.4. Fulfilment of commitments:

- concerns (reasonable opinion regarding the absence of an organizational structure, resource base or quality assurance system of the pharmacovigilance system at the disposal of

the Marketing Authorization Holder of the registration certificate) about the status or fulfilment of risk management plan commitments;

- delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization;

- poor quality of reports requested as specific obligations;

#### 4.2.1.2.2.5. Inspections:

- delays in the implementation or inappropriate implementation of corrective and preventive actions;

- information such as non-compliance with legal requirements of the member states, International Treaties and legislation of the Union;

- inspection of information received from other competent authorities of Member States, which may highlight issues of non-compliance in pharmacovigilance system;

#### 4.2.1.2.2.6. Others:

- concerns following review of the Pharmacovigilance system master file;

- other sources of information or complaints, indicating that the marketing authorisation holder does not have a pharmacovigilance system or a system for ensuring its quality.

#### *4.2.1.3 Pre-authorization inspections*

4.2.1.3.1. Pre-authorization pharmacovigilance inspections are inspections performed before a marketing authorization is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorization application. Pre-authorization inspections are not mandatory, but may be requested in specific circumstances. Principles for requesting pre-authorization inspections should be developed beforehand to avoid performing unnecessary inspections, which may delay the granting of a marketing authorization.

The following factors shall be taken into account upon consideration of feasibility and validity of pre-authorization inspections:

- the applicant has not previously operated a pharmacovigilance system within the Eurasian Economic Union or is in the process of establishing a new pharmacovigilance system;

- previous information (for instance, inspection history and non-compliance notifications or information from other competent authorities of Member States) indicates that the applicant has a poor history or culture of compliance with the pharmacovigilance system requirements. If the marketing authorization holder has a history of serious and / or persistent pharmacovigilance non-compliance, a pre-authorization pharmacovigilance inspection may be one mechanism to confirm that corrections/improvements have been made to the system;

- due to product-specific safety concerns, it may be considered appropriate to examine the applicant's ability:

- to implement product specific risk - minimization activities;
- to meet specific safety conditions which may be imposed;
- to manage routine pharmacovigilance for the product causing a safety profile concern.

A risk assessment based on a combination of product-specific and system-related issues should be performed before a pre-authorization pharmacovigilance inspection is requested.

4.2.1.3.2. If the outcome of the pre-authorization inspection of the pharmacovigilance system raises concerns about the applicant's ability to comply with the requirements established for the pharmacovigilance system established by applicable legislation of member states and Good Pharmacovigilance Practice of EAEU, the following recommendations may be considered by the competent authority:

- a) non-approval of the marketing authorization;
- b) a re-inspection prior to approval of the marketing authorization to confirm that critical findings and recommendations have been addressed;
- c) granting of the marketing authorization with the recommendation to perform an early post-authorization pharmacovigilance inspection.

#### 4.2.1.4. *Post-authorization inspections*

Post-authorization pharmacovigilance inspections are inspections performed after a marketing authorization is granted and are intended to examine whether the marketing authorization holder complies with its pharmacovigilance obligations. Post-authorization pharmacovigilance inspections can be any of the types mentioned under 4.2.1.1 and 4.2.1.2.

#### 4.2.1.5. *Announced and unannounced inspections*

The majority of pharmacovigilance system inspections will be announced, i. e. notified in advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on occasion, it may be appropriate to conduct unannounced inspections or to announce an inspection to the inspected party at short notice (for instance, when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short time frame due to urgent safety reasons).

#### 4.2.1.6. *Re-inspections*

A re-inspection may be conducted on a routine basis as part of a routine pharmacovigilance inspection programme. Risk factors should be assessed in order to prioritize re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions and measures taken to address findings and to evaluate ongoing compliance with the pharmacovigilance obligations and requirements



established for the pharmacovigilance system, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriately corrective and preventive actions in response to an earlier inspection.

#### *4.2.1.7. Remote inspections*

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorization holder or other organizations employed by the marketing authorization holder to perform pharmacovigilance functions. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances. Such approaches are taken at the discretion of the inspectors and in agreement with the competent authority commissioning the inspection. The logistical aspects of the remote inspection should be considered following liaison with the marketing authorization holder. A remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection has revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

#### **4.2.2. Inspection planning**

4.2.2.1. Pharmacovigilance inspection planning should be based on a systematic and risk - based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. A risk - based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

4.2.2.2. Factors which may be taken into consideration by the competent authorities of Member States when establishing pharmacovigilance inspection programmes may include:

- a) inspection related factors:
  - non-compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP, and GDP);
  - re-inspection date recommended by the inspectors or assessors as a result of a previous inspection;
- b) factors related to medicinal products:
  - marketing authorization for a medicinal product with additional pharmacovigilance activities or risk - minimization activities;
  - marketing authorization for a medicinal product with requirement for post-authorization safety studies or designation for additional monitoring;

- marketing authorization for a medicinal product (or products) with large sales volume, i. e. products associated with potentially large patient exposure;
  - medicinal product(s) with limited alternative in the market place of the Eurasian Economic Union member states;
- c) marketing authorization holder related factors:
- marketing authorization holder that has never been subject to a pharmacovigilance inspection;
  - marketing authorization holder with many medicinal products in the markets of the Eurasian Economic Union member states;
  - marketing authorization holder with no previous marketing authorizations in the Eurasian Economic Union member states;
  - negative information with regard to compliance with legal requirements and/or product safety concerns raised by competent authorities of Member States of the Eurasian Economic Union member states or other countries, as well as competent authorities of Member States in other areas regulating the circulation of medicinal products (i. e. GCP, GMP, GLP, and GDP);
  - changes in the organizational structure of the marketing authorization holder organization, such as mergers and acquisitions;
- d) pharmacovigilance system related factors:
- marketing authorization holder with sub-contracted pharmacovigilance activities (function of the qualified person responsible for pharmacovigilance in the Eurasian Economic Union (QPPV), reporting of safety data etc.) and / or multiple organizations employed to perform pharmacovigilance activities;
  - change of QPPV since the last inspection;
  - changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database, as well as information about transferred or migrated data;
  - changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted;
  - delegation or transfer of Pharmacovigilance System Master File management.

4.2.2.3. The competent authorities of Member States may solicit information from marketing authorization holders for risk - based inspection planning purposes if it is not readily available elsewhere.

#### ***4.2.3. Sites to be inspected***

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorization holder may be inspected, in order to confirm their capability to support the marketing authorization holder's compliance with

pharmacovigilance obligations and legal requirements established for the pharmacovigilance system. The sites to be inspected may be located in the Eurasian Economic Union member states or outside the EAEU. Inspections of sites outside the Eurasian Economic Union might be appropriate where the main pharmacovigilance centre, databases and / or pharmacovigilance activities are located outside the Eurasian Economic Union. The type and number of sites to be inspected should be selected appropriately to ensure that the key objectives within the scope of the inspection are met.

#### ***4.2.4. Scope of inspection***

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by the competent authorities of Member States of the Eurasian Economic Union member states and the type of inspection. The following elements should be considered when preparing the scope of the inspection:

- a) information supplied in the Pharmacovigilance System Master File;
- b) information concerning the functioning of the pharmacovigilance system, for instance system compliance data available from the competent authority;
- c) specific inspection triggers (see Paragraph 4.2.1.2);

##### *4.2.4.1 . Routine pharmacovigilance inspections*

Routine inspections of the pharmacovigilance system should examine compliance with legal requirements of the member states, International Treaties and legislation of the Union, and the scope of such inspections should include the following elements, as appropriate:

- a) procedures to handle individual case safety reports (ICSRs):
  - collecting, receiving and exchanging reports - from all types of sources, sites and departments within the pharmacovigilance system, including from those organizations employed to fulfil the marketing authorization holder's pharmacovigilance obligations and departments other than drug safety;
  - assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality assessment;
  - follow-up and outcome recording, for example final outcome of cases of exposure to a medicinal product in pregnancy and medical confirmation of consumer reported events;
  - reporting to the relevant competent authorities of Member States according to the legal requirements of the member states, International Treaties and legislation of the Union for various types of reported ICSRs;
  - record keeping and archiving for ICSRs;
- b) periodic safety update reports (PSURs) (if applicable):
  - completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;

- addressing safety profile related topics, providing relevant analyses and actions;
  - formatting according to applicable legal requirements;
  - timeliness of submissions;
- c) ongoing safety profile evaluation:
- use of all relevant sources of information for signal detection;
  - appropriately applied methodology concerning analysis of information;
  - appropriateness of investigations and follow-up actions, for instance the implementation of recommendations following data review;
  - implementation of the risk management plan or other commitments;
  - timely identification and provision of complete and accurate data to the competent authorities of Member States, in particular in response to specific requests for data;
  - implementation of approved changes to safety communications and product information;
- d) interventional (where appropriate) and non-interventional clinical trials:
- reporting suspected unexpected serious adverse reactions in accordance with the legal requirements of the Eurasian Economic Union member states;
  - receiving, recording, and assessing adverse drug reactions cases from interventional and non-interventional clinical trials;
  - submission of study results and relevant safety information in the form of reports prepared in accordance with the legal requirements of the Eurasian Economic Union member states;
  - appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
  - the inclusion of study data in ongoing safety profile evaluation for medicinal products;
- e) pharmacovigilance system procedures:
- QPPV roles and responsibilities, for instance access to the quality system, the pharmacovigilance system master file, performance metrics and system indicators, audit and inspection reports, and their ability to take action to improve compliance;
  - the roles and responsibilities of the marketing authorization holder in relation to the pharmacovigilance system;
  - accuracy, completeness, and maintenance of the pharmacovigilance system master file;
  - quality and adequacy of training, qualifications and experience of staff;
  - coverage and adherence to the quality system in relation to the pharmacovigilance system, including quality control and quality assurance processes;
  - fitness for purpose of computerised systems for the performance of specific functions;
  - contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.

The inspection may include the assessment of compliance of implemented risk –

minimization activities with the established requirements.

#### *4.2.4.2 For cause inspections*

The scope of the inspection will depend on the specific triggers. Some, but not all of the system aspects listed in Paragraph 4.2.4.1. and below, may be relevant:

- a) QPPV involvement and awareness of product-specific issues;
- b) in-depth examination of processes, decision-making procedures, communications and actions relating to a specific trigger and / or medicinal product.

#### *4.2.4.3 Re-inspections*

4.2.4.3.1. For the scope of a re-inspection, the following aspects should be considered:

- a) review of the status of the system and / or corrective and preventive action plan resulting from the previous pharmacovigilance inspection;
- b) review of significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection (for instance, change in the pharmacovigilance database, company mergers or acquisitions, significant changes in contracted activities, change in QPPV);
- c) review of process and / or product-specific issues identified from the assessment of information provided by the marketing authorization holder, or not covered in a prior inspection.

4.2.4.3.2. The scope of re-inspection will depend on results obtained in previous inspections, and it may be appropriate to broaden its scope based on a number of factors (for instance, time that has elapsed since the previous inspection or scope of the previous inspection, as appropriate).

#### **4.2.5 Inspection process**

4.2.5.1. Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with inspection procedures performed in the Eurasian Economic Union member states. Improvement and harmonization of inspection conduct is promoted by agreed processes and procedures, joint inspections and sharing of experience as well as training by competent authority inspectorates.

4.2.5.2. The procedures on pharmacovigilance inspections of pharmacovigilance systems should cover the following processes:

- a) sharing of information;
- b) inspection planning;
- c) pre-authorization inspections;
- d) coordination of pharmacovigilance inspections in the Eurasian Economic Union;

- e) coordination of third country inspections (including inspections of contractors in third countries);
- f) preparation of pharmacovigilance inspections;
- g) conduct of pharmacovigilance inspections;
- h) reporting of pharmacovigilance inspections and inspection follow-up;
- i) communication and prioritization of pharmacovigilance inspections and findings;
- j) record-keeping and archiving of documents obtained or resulting from pharmacovigilance inspections;
- k) unannounced inspections;
- l) sanctions and regulatory or enforcement measures in case of serious non-compliance with applicable legal requirements and Good Pharmacovigilance Practice;
- m) recommendations on the training of inspectors performing pharmacovigilance inspections and exchange of experience.

4.2.5.3. New procedures may also be developed when necessary.

#### ***4.2.6 Inspection follow-up***

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. The following follow-up actions should be considered, as appropriate:

- a) review of the marketing authorization holder's corrective and preventive action plan;
- b) review of the periodic progress reports, when deemed necessary;
- c) re-inspection to assess appropriate implementation of the corrective and preventive action plan;
- d) requests for submission of previously un-submitted data; submission of variations (for instance, to amend the product information); submission of impact analyses (for instance, following review of data that were not previously considered during routine signal detection activities);
- e) requests for issuing safety communications, including amendments of marketing and / or advertising information;
- f) requests for a meeting with the marketing authorization holder to discuss the deficiencies / nonconformities and their impact on the action plan;
- g) communication of the inspection findings to other competent authorities of Member States;
- h) other product-related actions depending on the impact of the deficiencies / nonconformities and the outcome of follow-up actions (this may include recalls or actions relating to the marketing authorizations or clinical trial authorizations).

#### **4.2.7 Regulatory actions and sanctions**

4.2.7.1. Under the legislation of the Eurasian Economic Union member states, in order to protect public health, the competent authorities of Member States are obliged to ensure compliance of marketing authorization holders with pharmacovigilance obligations. When non-compliance with pharmacovigilance obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative public health impact of the deficiencies/non-compliances, but any instance of deficiency / non-compliance may be considered for enforcement action. The Eurasian Economic Union member state concerned shall take the necessary measures to ensure that a marketing authorization holder is subject to effective, proportionate, and dissuasive penalties.

4.2.7.2. In the event of non-compliance, possible regulatory options include the following, in accordance with Guidelines and, as applicable, rules set in the legislation of the Eurasian Economic Union member states:

- a) education and facilitation: national competent authorities of Member States may communicate with marketing authorization holder representatives (for instance, in a meeting) to summarize the identified non-compliances, to clarify the legal requirements and the expectations of the competent authority, and to review the marketing authorization holder's proposals for corrective and preventive actions;
- b) provision of information to other competent authorities of Member States under the framework of confidentiality arrangements;
- c) inspection: non-compliant marketing authorization holders may be inspected to determine the extent of their non-compliance with legal requirements of the member states, International Treaties and legislation of the Union, and then re-inspected to ensure that compliance is achieved;
- d) warning letter, non-compliance statement or infringement notice issued by competent authorities of Member States with identification guideline that has been breached, reminding marketing authorization holders of their pharmacovigilance obligations or specifying the measures that the marketing authorization holder must take and in what timeframe in order to rectify the non-compliance and in order to prevent a further case of non-compliance;
- e) competent authorities of Member States may consider making public a list of marketing authorization holders found to be seriously or persistently non-compliant with regard to the requirements of the pharmacovigilance legislation;
- f) actions against a marketing authorization or marketing authorization application, such as:
  - urgent restrictions related to the safety profile of a medicinal product;

- suspension or revocation of the marketing authorization;
  - delays in approvals of new marketing authorization applications until corrective and preventive actions have been implemented;
  - requests for pre-authorization inspections of the pharmacovigilance system;
- g) product recalls: for instance, where important safety warnings have been omitted from the product information;
- h) action relating to marketing or advertising information;
- i) protocol amendments or suspension of clinical trials due to product-specific safety profile changes;
- j) administrative penalties according to legislation of Member States.

#### ***4.2.8. Qualification and training of inspectors***

Inspectors who are involved in the conduct of pharmacovigilance inspections should be officials of the competent authorities of Member States of the Eurasian Economic Union member states or individuals appointed in accordance with national regulation, and should follow the provisions of the national competent authority. It is recommended that inspectors are appointed based upon their experience and the minimum requirements defined by the national competent authority. The inspectors should undergo training to the extent necessary to ensure their competence in the skills required for preparing, conducting, and reporting inspections. They should also be trained in pharmacovigilance processes and requirements in such way that they are able, if not acquired by their experience, to comprehend the different aspects of a pharmacovigilance system.

#### ***4.2.9. Quality management of the pharmacovigilance inspection process***

Quality of the pharmacovigilance inspection process is managed by the national competent authorities of Member States and covered by their pharmacovigilance quality systems, meaning that the process is also subject to audit.

### **4.3 Operation of the Eurasian Economic Union network**

#### ***4.3.1. Sharing of information***

The competent authorities of Member States of the Eurasian Economic Union member states shall cooperate to facilitate the exchange of information on pharmacovigilance system inspections and in particular:

- a) information on inspections planned and conducted in order to avoid unnecessary repetition and duplication of activities in the Eurasian Economic Union as well as to optimize the inspection resources;
- b) information on the scope of the inspection in order to focus future inspections;



c) information on the outcome of the inspection, in particular when the outcome is that the marketing authorization holder does not comply with the requirements laid down in pharmacovigilance legislation and Good Pharmacovigilance Practice. Information concerning critical and / or major findings and a summary of the corresponding corrective and preventive actions with their follow-up should be exchanged by the competent authorities of Member States.

#### **4.4. Role of Marketing Authorization Holders**

Marketing authorization holders with products authorized in Eurasian Economic Union member states are subject to pharmacovigilance inspections. Marketing authorization holders have the following responsibilities in relation to inspections:

- always to be inspection-ready as inspections may be unannounced;
- to maintain and make available to the inspectors on request, no later than 7 calendar days after the receipt of a request, the pharmacovigilance system master file;
- to ensure that the sites selected for inspection, which may include organizations employed by the marketing authorization holder to perform pharmacovigilance activities, agree to be inspected before the inspection is performed;
- to make available to the inspectors any information and / or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection;
- to ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;
- to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and / or major deficiencies / non-compliances.

#### **4.5. Inspection fees**

Inspection fees will be charged in accordance with the fee regulations, as required by the legislation of the Eurasian Economic Union Member states

## 5. AUDIT OF PHARMACOVIGILANCE SYSTEM

### 5.1. Structures and Processes

#### *5.1.1. Audit of the pharmacovigilance system and its objectives.*

5.1.1.1. The aim of pharmacovigilance system audit is a verification of the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, by analysis and evaluation of objective evidence, including its quality system.

5.1.1.2. An audit is a systematic, disciplined, independent and documented process for obtaining and evaluating objectively evidence characterizing a pharmacovigilance system operation to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes. Audit evidence consists of records, statements or other information, which are relevant to the audit criteria and verifiable. Audit criteria are the standards of performance and control against which the auditee and its activities will be assessed. In the context of pharmacovigilance system, audit criteria should reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in the legislation of member states and good pharmacovigilance practice

#### *5.1.2. The risk-based approach to pharmacovigilance system audits*

A risk-based approach is one that uses techniques to determine the areas of risk. Risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking into account the severity of its outcome and/or probability of non-detection by other methods. The risk-based approach to audits focuses on the areas of highest risk to the organization's pharmacovigilance system, including its quality system for pharmacovigilance system. In the context of pharmacovigilance, the risk to public health is of prime importance. Risk is assessed at the following stages:

- strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by senior management;
- tactical level audit planning resulting in an audit program, setting audit objectives, and the scope of the audit;
- operational level audit planning resulting in an audit plan for individual audit engagements, prioritizing audit tasks based on risk assessment and utilizing risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations.

Risk assessment should be documented for strategic, tactical and operational planning of audit activity of pharmacovigilance audit activity in the organizations.

##### *5.1.2.1 .Strategic level audit planning*

5.1.2.1.1. The audit strategy is a high level statement of how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.

5.1.2.1.2. The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system including:

- a) all pharmacovigilance processes and tasks;
- b) the quality system for pharmacovigilance activities;
- c) interactions and interfaces with other departments, as appropriate;
- d) pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties, such as contract organisations and other Marketing Authorization Holders).

5.1.2.1.3. Risk factors that could be considered for the purposes of a risk assessment, including, but not limited to the following:

- a) Changes to pharmacovigilance legislation of member states or guidance on GVP;
- b) major re-organization or other transformations of the pharmacovigilance system, mergers, acquisitions;
- c) change in key managerial function(s);
- d) risk to availability of adequately trained and experienced pharmacovigilance staff (e.g. due to significant turn-over of staff, deficiencies in training processes, re-organisation, increase in volumes of work);
- e) significant changes to the pharmacovigilance system since the previous audit (e.g. introduction of a new database for pharmacovigilance activities or a significant upgrade to the existing database, changes to processes and activities in order to address new or amended regulatory requirements);
- f) first medicinal product on the market (for a marketing authorisation holder);
- g) medicinal product(s) on the market with specific risk minimisation measures or other specific safety conditions (for examples, requirements for additional monitoring);
- h) criticality of the process, e.g.:

for competent authorities: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health [*healthcare system*];

for marketing authorisation holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the

marketing authorisation holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the marketing authorisation holder, in addition to considering the other factors included in this list;

i) outcome of previous audits (if the area/process has previously been audited, the findings of the previous audit);

j) identified procedural gaps relating to specific areas/processes;

k) Other organizational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively impact upon pharmacovigilance activities.

#### *5.1.2.2. Tactical level audit planning*

5.1.2.2.1. An audit program is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long-term audit strategy. The audit program should be approved by upper management with overall responsibility for the operational and governance structure.

5.1.2.2.2. The risk-based audit program should be based on an appropriate risk assessment and should focus on the assessment of following aspects:

a) The quality system for pharmacovigilance system;

b) Critical processes in pharmacovigilance system;

c) Key control systems relied on pharmacovigilance activities;

d) Areas identified as high risk, after control procedures and measures of risk minimization measures have been introduced.

5.1.2.2.3. The risk-based audit program should also take into account the results of previous audits in the areas with insufficient coverage, high-risk areas and areas identified by specific requests from management and/or persons responsible for pharmacovigilance system.

5.1.2.2.4. The audit program documentation should include a brief description of the plan for each audit to be conducted, including its scope and objectives. The rationale for the timing, periodicity and scope of the individual audits which form part of the audit program should be based on the documented risk assessment. Risk-based audits of pharmacovigilance system should be performed at regular intervals in accordance with legal requirements of the member states, International Treaties and legislation of the Union. The introduction of substantiated amendments into an audit program should be duly documented.

#### *5.1.2.3. Operational level audit planning and reporting*

##### *5.1.2.3.1. Planning and fieldwork*

The organization should ensure that written procedures are in place regarding the

planning and conduct of individual audits. Timeframes for all the measures required for the performance of an individual audit should be settled in the relevant audit related procedures. The organization should ensure that audits are conducted in accordance with the written procedures, in line with this section GVP.

Individual audits of pharmacovigilance system should be undertaken in line with the approved risk-based audit program (refer to 5.1.2.2.). When planning individual audits, the auditor identifies and assesses the risks relevant to the area under review and employs the most appropriate sampling and testing methods. The method of audit is duly documented in an audit plan.

#### *5.1.2.3.2. Reporting*

The findings of the auditors should be documented in an audit report and be communicated to management in a timely manner. The audit process should include mechanisms for communicating the audit findings to the auditee and receiving feedback, and submitting the audit reporting to management and relevant parties, including those responsible for pharmacovigilance system, in accordance with the EAEU countries legislative requirements, international acts and contracts comprising EAEU law and recommendations on audit of pharmacovigilance system. Audit findings should be reported in line with their relative risk level and should be classified in order to indicate their criticality to risks impacting the pharmacovigilance system, processes and parts of processes. The classification system should be defined in the description of the quality system for pharmacovigilance, and should take into consideration the thresholds noted below which should be used in further reporting:

- critical is a fundamental deficiency/non-compliance in one or more processes or performed procedures of pharmacovigilance system that adversely affects the whole pharmacovigilance system and/or the rights, safety and well-being of patients, and/or that poses a potential risk to public health and/or represents a serious violation of applicable EAEU legislative requirements, international acts and contracts comprising EAEU law;

- major is a significant deficiency/non-compliance in one or more processes or performed procedures of pharmacovigilance system, or a fundamental deficiency in part of one or more pharmacovigilance processes or performed procedures that adversely affects the whole process and/or could potentially affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable EAEU legislative requirements, international acts and contracts comprising EAEU law, which is however not considered serious.

- minor is a deficiency/non-compliance in the part of one or more processes or performed procedures or non-performed procedures of pharmacovigilance system that is not expected to

adversely affect the whole pharmacovigilance system or process and/or the rights, safety and well-being of patients.

Issues that need to be urgently addressed should be communicated in an expedited manner to the auditee's management and the upper management.

#### *5.1.2.4. Actions based on audit findings and follow-up of audits*

5.1.2.4.1. Actions specified in this section of the guidance, such as prompt actions, operative actions, actions in reasonable timeframe and issues that require urgent decision taking or urgent communicating, are intended to be executed within timelines, which are proper, appropriate and adequate to relative risk for a pharmacovigilance system. It is necessary to prioritize the corrective and preventive actions to eliminate the revealed critical and significant deficiencies/non-compliances. The exact timeframes for actions related to a revealed critical deficiency/non-compliance may vary depending on the character of findings and the planned action.

5.1.2.4.2. The management of the organization is responsible for ensuring that the organization has a mechanism in place to adequately address the issues connected with pharmacovigilance system audit findings. The set of measures should include the root cause analysis and impact analysis of the identified audit findings, and preparation of a corrective and preventive action plan.

5.1.2.4.3. Upper management and those charged with management responsibilities should ensure that all the necessary effective measures are implemented to address audit findings. The implementation of coordinated actions should be monitored in a systematic way. Information on the progress of implementation of corrective and preventive measures should be communicated on a periodic basis to senior management according to the planned actions. Evidence of completion of the complex of corrective and preventive measures should be duly recorded. Capacity for follow-up audits should be included into the audit program. They should be carried out as deemed necessary, in order to verify the completion of coordinated actions.

### ***5.1.3 Quality system and record management practices***

#### *5.1.3.1. Competence of auditors and quality management of audit activities*

##### *5.1.3.1.1. Independence and objectivity of audit work and auditors*

The organization should assign a specific person responsible for the pharmacovigilance audit activities. . Pharmacovigilance system audit activities should be independent. The organization's management should ensure and document the auditors' independence and objectivity.

Auditors should be free from interference in determining the scope of auditing, performing pharmacovigilance system audit and communicating audit results. The main

reporting line should be to the upper management with overall responsibility for operational and governance structure that allows the auditor(s) to fulfil their responsibilities and to provide independent, objective audit opinion. Auditors can consult with experts, personnel involved in pharmacovigilance processes, and with the person responsible for pharmacovigilance; while maintaining an unbiased attitude and absence of influence on the objectivity and quality of works performed.

*5.1.3.1.2. Qualifications, skills and experience of auditors and continuing professional development.*

Auditors should demonstrate and maintain proficiency in terms of the knowledge, skills and abilities required to effectively conduct and/or participate in pharmacovigilance system audit activities. The auditors should have skills, abilities and knowledge in:

- a) audit principles, procedures and techniques;
- b) applicable laws, regulations and other requirements relevant to pharmacovigilance system;
- c) pharmacovigilance activities, processes and procedures;
- d) management systems;
- e) organizational systems.

*5.1.3.1.3. Evaluation of the quality of audit activities*

Evaluation of audit work can be undertaken by means of ongoing and periodic assessment of all audit activities, auditee feedback and self-assessment of audit activities (e.g. quality assurance of audit activities, compliance to code of conduct, audit program, and audit procedures).

*5.1.3.2 Audits undertaken by outsourced audit service providers*

Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organization. Where the organization decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of this GVP and perform pharmacovigilance audits:

- a) the requirements and preparation of the audit risk assessment, the audit strategy and audit program and individual audit tasks should be specified to the outsourced service provider, by the organization, in writing;
- b) the scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organization, in writing;
- c) the organization should obtain document assurance of the independence and objectivity of outsourced audit service providers;
- d) the outsourced audit service provider should also follow the relevant parts of this GVP.

### *5.1.3.3. Retention of audit reports*

Retention of the audit report and evidence of completion of action needs to be in line with the requirements stipulated in section 2.

## **5.2. Requirements to perform an audit**

### ***5.2.1. Marketing authorization holders***

#### *5.2.1.1. Requirement to perform an audit*

The marketing authorization is required to perform regular risk-based audit of their pharmacovigilance system including the audits of the pharmacovigilance system quality system to ensure that the quality system complies with the quality system requirements. The dates and results of audits and follow-up audits shall be duly documented.

##### *5.2.1.1.1. The qualified person responsible for pharmacovigilance in the EAEU*

The QPPV should receive pharmacovigilance system audit reports, and provide information to the auditors relevant to the risk assessment, including knowledge of status of corrective and preventive actions. The QPPV should be notified of any audit findings relevant to the pharmacovigilance system in the EAEU irrespective of where the audit was conducted.

#### *5.2.1.2. Competent authorities of Member States of the EAEU member-states*

##### *5.2.1.2.1. Requirements to conduct of audit*

The competent authority shall regularly perform independent inspection of the tasks of the national pharmacovigilance system and a regular audit of its pharmacovigilance system and the risk-based audits of the quality system to provide compliance of the quality system with specified requirements. The dates and findings of the audits conducted and the follow-up audits should be duly documented.

##### *5.2.1.2.2. Recognized methodology*

To provide the coordinated and harmonized planning, implementation and reporting, the audits conducted in the competent authorities of Member States of the EAEU member-states should be based on the recognized terminology and methodology.

### ***5.2.2. Requirements to audit reporting***

#### *5.2.2.1. Reporting of a marketing authorization holder*

5.2.2.1.1. A marketing authorization holder shall place a notice concerning critical and major findings of any audit relating to the pharmacovigilance system in the pharmacovigilance system master file. Based on the audit findings the marketing authorization holder shall provide the preparation and implementation of a corresponding plan which should specify in details corrective and preventive measures. Once the corrective and preventive actions have been fully implemented, the note may be removed from the master file. Objective evidence is required in



order that any note of audit findings can be removed from the pharmacovigilance system master file.

5.2.2.1.2. A marketing authorization holder should provide the inclusion of a list of all scheduled and conducted audits into the annex to the pharmacovigilance system master file and the performance of all planned audits subject to the obligations on reporting set by legislation, GVP and internal reporting rules. The dates and findings of the conducted audits and the follow-up audits shall be duly documented.

#### 5.2.2.2. Reporting by competent authorities in the EAEU member-states

Competent authorities in the member-states should ensure that they comply with reporting commitments on submitting reports of the audits in line with legal requirements of the member states, International Treaties and legislation of the Union EAEU member-states legislation, and internal reporting rules.

#### **5.2.3. Confidentiality**

Documents and information collected by an internal auditor should be treated according to requirements of the EAEU member-state legislation, including legislation concerning personal data and confidential information protection.

## **6. RISK MANAGEMENT SYSTEM**

### **6.1. Introduction**

The risk management system consists of three stages which are inter-related and re-iterative:

- Characterization of the safety profile of the medicinal drug, including both known and unknown aspects.
- Planning of pharmacovigilance activities to characterize risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal drug.
- Planning and implementation of risk minimization and mitigation and assessment of the effectiveness of these activities.

### **6.2. Structures and processes**

#### ***6.2.1. Principles of risk management***

The overall aim of the risk management process is to ensure that the benefits of a particular medicinal drug (or a series of medicinal drugs) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks. The risk management system is cyclical by nature and consists of recurrent stages of the determination and analysis of risks and benefits, assessment of the risk-benefit balance and determination of the possibility for optimization, selection and planning of methods for risk characterization/minimization, introduction of risk characterization/ minimization measures, and data collection with monitoring of the efficacy of measures taken.

#### ***6.2.2. Responsibilities for risk management within an organization***

The principle organizations directly involved in medicinal drugs' risk management planning are marketing authorization holders and the competent authorities of the Eurasian Economic Union member states who regulate the circulation of medicinal drugs.

##### ***6.2.2.1. Marketing authorization holders***

In relation to risk management of its medicinal drugs, a marketing authorization holder is responsible for the following:

- a) ensuring that it constantly monitors the risks of its medicinal drug(s) in compliance with relevant legislation of the Eurasian Economic Union member states and reports obtained results to the appropriate competent authorities of Member States of the member states;
- b) taking all appropriate actions to minimize the risks of the medicinal drug and

maximize the benefits, including ensuring the accuracy of all information produced by the marketing authorization holder in relation to its medicinal drugs, and actively updating and promptly communicating it when new information becomes available.

*6.2.2.2. Competent authorities of Member States of the Eurasian Economic Union member states*

The general responsibilities of competent authorities of Member States of the member states in relation to the risk management process are:

a) constantly monitoring the benefits and risks of medicinal drugs, including assessing the adverse drug reaction reports submitted by marketing authorization holders, health care and pharmaceutical professionals, patients and, where appropriate, other sources of information;

b) taking appropriate regulatory actions to minimize the risks of the medicinal drug and maximize the potential benefits, including ensuring the accuracy and completeness of all information produced by the marketing authorization holders in relation to their medicinal drugs;

c) ensuring the implementation of risk minimization activities at a national level;

d) effectively communicating with stakeholders when new information becomes available. This includes providing information in an appropriate format to patients, health care and pharmaceutical professionals, patient groups, scientific societies, etc.;

e) ensuring that all marketing authorization holders (both of original and generic medicinal drugs) take appropriate risk minimization measures when a risk is identified;

f) providing information to other competent authorities of the member states, this includes notification of any safety activities in relation to a medicinal drug, including changes to the drug information of the original medicinal drug.

**6.2.3. Objectives of a risk management plan**

6.2.3.1. The risk management plan (RMP) contains information, which should fulfil the following requirements:

a) identify and characterize the safety profile of the medicinal drug(s);

b) indicate how to characterize further the safety profile of the medicinal drug(s) concerned;

c) document measures to prevent or minimize the risks associated with the medicinal drug, including an assessment of the effectiveness of those interventions;

d) document fulfilment of post-authorization drug safety obligations that have been imposed as a condition of the marketing authorization.

6.2.3.2. For the purpose of compliance with the requirements mentioned in the item

6.2.3.1 a RMP should also:

- a) describe known and unknown information about the safety profile of the concerned medicinal drug(s);
- b) indicate the level of certainty that efficacy shown in clinical trial target populations will be seen when the medicinal drug is used in the wider target populations seen in everyday medical practice and document the potential need for effectiveness studies in the post-authorization phase;
- c) determine the method of assessment of the effectiveness of risk minimization measures.

6.2.3.3. The RMP is a dynamic, stand-alone document, which should be updated throughout the life-cycle of the drugs. For drugs requiring submission of periodic safety update reports (PSURs), certain (parts of) modules of RMP may be used for PSUR purposes.

#### **6.2.4. *Structure of the risk management plan.***

The RMP consists of seven information parts:

- Part I. Drug overview;
- Part II. Safety specification;
- Module SI: Epidemiology of the indication(s) and target population(s);
- Module SII: Non-clinical part of the safety specification;
- Module SIII: Clinical trial exposure;
- Module SIV: Populations not studied in clinical studies/trials;
- Module SV: Post-authorization experience;
- Module SVI: Additional requirements for the safety specification;
- Module SVII: Identified and potential risks;
- Module SVIII: Summary of the safety concerns;
- Part III. Pharmacovigilance plan
- Part IV. Plans for post-authorization efficacy studies;
- Part V. Risk minimization measures (including evaluation of the effectiveness of risk minimization measures);
- Part VI. Summary of the risk management plan;
- Part VII. Annexes.

If the RMP covers several medicinal drugs, an individual part should be dedicated to each of these medicinal drugs.

#### **6.2.5. *Detailed description of each part of the RMP***

##### **6.2.5.1. *RMP part I “Drug(s) overview”***

This should provide the administrative information on the RMP, as well as an

overview of the medicinal drug(s) covered within it.

The information should include:

a) Active substance information:

- active substance(s) of the medicinal drug(s);
- pharmacotherapeutic group(s) (ATC code);
- name of the marketing authorization holder;
- date and country of first authorization worldwide (if applicable);
- date and country of first launch in medical practice worldwide (if applicable);
- number of medicinal drug(s) to which this RMP refers.

b) Administrative information on the RMP:

- data lock point of the current RMP;
- date submitted and the version number;
- list of all parts and modules of the RMP with the date and version of the

RMP when the part / module was last updated and submitted.

c) Information for each medicinal drug included in the RMP:

- trade name(s) in the Eurasian Economic Union member states;
- brief description of the medicinal drug (including the following: chemical class, summary of the mechanism of action, important information about its composition (for instance, the origin of the active substance of biologicals, relevant adjuvants for vaccines);
- indications (approved and proposed (if applicable));
- dosing regimen (approved and proposed (if applicable));
- pharmaceutical forms and strengths (approved and proposed (if applicable));
- global regulatory status by country (marketing authorization or marketing authorization refusal date, market placement date, current marketing authorization status, explanatory comments).

#### 6.2.5.2. RMP part II “Safety specification”

The purpose of this section is to provide a synopsis of the safety profile of the medicinal drug(s) and should include known safety-related information, as well as definitions of the profile sections where the safety has not been sufficiently investigated. The safety specification should be a summary of the important identified risks of a medicinal drug, important potential risks, and important missing information. The safety specification of the RMP will form the basis of the pharmacovigilance plan, and of the risk minimization plan.

The safety specification of the RMP includes eight sections:

- Module SI: Epidemiology of the indication(s) and target population(s);

- Module SII: Preclinical part;
- Module SIII: Clinical trial exposure;
- Module SIV: Populations not studied in clinical trials;
- Module SV: Post-authorization experience;
- Module SVI: Additional requirements for the safety specification;
- Module SVII: Identified and potential risks;
- Module SVIII: Summary of the safety concerns;

The safety specification can include additional elements, depending on the properties of the medicinal drug and its development and investigation program, including quality aspects and their impact on the medicinal drug safety and efficacy profile, risks associated with the particular formulation and other safety profile-modifying aspects.

*6.2.5.2.1. RMP module SI “Epidemiology of the indications and target population”*

The epidemiology of the indication(s) is the subject matter of the description and assessment in this Section. This description should include incidence, prevalence, mortality, relevant co-morbidities in the target population, and should, whenever possible, be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be evaluated and described as well. Information should be provided on the important co-morbidities in the target population and on the possible effects of the medicinal drug on concomitant conditions. The RMP should include a statement of the intended purpose and impact of the medicinal drug, for instance, whether it is intended to prevent disease, to prevent particular serious outcomes due to certain conditions, or to reduce progression of a chronic disease. A summary of the role of the medicinal drug in the therapeutic arsenal should be provided as well.

*6.2.5.2.2. RMP module SII “Preclinical part”*

This RMP module should present a summary of the important non-clinical safety findings, for instance:

- toxicity (key issues identified in non-clinical studies, e.g. repeat-dose toxicity, reproductive toxicity, developmental toxicity, teratogenicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
  - general pharmacology data (e.g. cardiovascular effects, including QT interval prolongation, nervous system, etc.);
  - drug interaction data;
  - other toxicity-related information.

Significant areas of toxicity, and the relevance of the findings to the use in humans, should be discussed in this section. The significance of such data will depend on the medicinal

drug properties, specifics of the target population and experience with other similar compounds or therapies in the same drug class. Besides, quality aspects if relevant to the safety profile of the medicinal drug (e.g. important information on the active substance or its impurities, for instance, genotoxic impurities) should be discussed. If a drug is intended for use in women of child-bearing age, data on the redruggive and developmental toxicity should be explicitly mentioned and the implications for use of the respective medicinal drug in this population discussed. For other special populations depending upon the indication and target population, consideration should be given to whether specific non-clinical data needs exist.

6.2.5.2.3. *RMP module SIII “Clinical trial exposure”*

Data on the patients studied in clinical studies/trials should be provided in this module (what patient groups were enrolled to investigate the medicinal drug). This data should be provided in the format most appropriate for analysis, e.g. tables or graphs. The size of the study population should be detailed using both numbers of patients and patient time (patient-years, patient-months) during which study subjects were exposed to the medicinal drug. Information on the populations included in the clinical studies/trials should also be stratified for relevant categories and also by the type of study/trial (randomized blinded trial population only and all clinical trial populations). Stratifications of population-based subgroups would normally include:

- age and gender;
- indications;
- dosing regimen;
- racial origin.

Duration of exposure should be provided either graphically (by plotting numbers of patients against time) or in tabular format.

The exposure of special populations (pregnant women, breast-feeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms) should be provided as appropriate. The degree of renal, hepatic, or cardiac impairment should be specified, as well as that of the genetic polymorphism.

When presenting age data, categories should be chosen which are relevant to the target population. Pediatric data and the data on elderly patients should be stratified by conventionally used age categories (such as 65 – 74 years, 75 – 84 years, and 85+ years for elderly patients). For teratogenic medicinal drugs, stratification into age categories relating to child-bearing potential is appropriate for the female population. Final results should be pooled, totals should be provided at the end of each table/chart as appropriate.

Unless clearly relevant, clinical study data should not be presented by individual trial

but should be pooled by graph and section as appropriate. Where patients have been enrolled in more than one trial (for instance, open label extension study following a clinical trial), they should only be included once in the age /sex /ethnic origin tables. Where differences in the total numbers of patients arise between tables, the tables should be annotated to reflect the reasons for discrepancy.

When the RMP is being submitted with an application for a new indication, the clinical trial data for the new dosage form or route of administration specific to the application should be presented separately at the start of the section, as well as being included in the summary tables.

#### 6.2.5.2.4. RMP module SIV “Populations not studied in clinical studies/trials”

RMP module SIV should discuss which sub-populations within the expected target population have not been studied or have only been studied to a limited degree in the clinical study population. Limitations of the clinical studies/trials should also be presented in terms of the relevance of the inclusion and exclusion criteria in relation to the target population, as well as differences that may arise through trial settings (for instance, hospital or general practice). The conclusions, with respect to predicting the safety of the medicinal drug in target populations, should be based on accurate and detailed assessment of the limitations of available clinical study data or their absence for some of the subgroups. In addition, the limitations of the clinical study database should be discussed with regard to the detection of adverse drug reactions due to:

- number of enrolled study subjects;
- cumulative exposure (e.g. specific organ toxicity);
- long-term use (e.g. carcinogenicity assessment).

Where the missing information could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.

6.2.5.2.4.1. Populations to be considered for discussion should include (but might not be limited to):

- Pediatric population – children (from birth to 18 years of age with consideration given to the different age categories, or, if justified, to other developmentally meaningful groups i.e. taking into consideration specific development periods);

- Elderly patients. Effects of use of medicinal drugs in patients over the age of 65 should be assessed – with appropriate consideration given to use in the older end of the age spectrum of the group. The assessment of the effects of co-morbidity or particular impairments (e.g. renal, hepatic) as applied to this population subgroup is made with regard to several possible concurrent factors, such as multiplex co-morbidity and multi-drug therapy which make a



concurrent impact which modifies the safety profile of a medicinal drug. Consideration of whether particular laboratory screening should be performed routinely before use of the medicinal drug in patients of this patient subgroup should be assessed. In particular, any adverse reactions which might be of special concern in the elderly, e.g. dizziness or central nervous system effects, should be explored;

- Pregnant or breastfeeding women. If the target population includes women of child-bearing age, the medicinal drug effects on pregnancy and/or breast-feeding should be considered. If the medicinal drug is not specifically intended for use during pregnancy, outcomes of any pregnancies which have occurred during clinical studies of the medicinal drug should be assessed. If the use of contraceptives was inclusion criteria for the clinical study, the discussion on gestation should also include an analysis of the reasons why the contraceptive measures in place failed (if applicable) and the effects for use under less controlled conditions of everyday medical practice;

- Patients with hepatic impairment;

- Patients with renal impairment;

- Patients with other relevant co-morbidities (e.g. cardiovascular pathology, immunodeficiency conditions);

- Patients with disease severity different from that revealed in clinical studies. Any experience of use in patients with different disease severities should be considered, particularly if the proposed indication is restricted to those patients with a specific disease severity.

- Patient subgroups with known and relevant genetic polymorphism. The extent of pharmacogenetic effects, the use in patients with unknown or different genotypes and the effects of genetic biomarker use in the target patient group should be considered. Possible impact on target population is subject to assessment and it should be determined what a safety problem the use of a medicinal drug in patients with an unknown or different genotype may present.

If a potentially clinically important genetic polymorphism has been identified but not fully studied in the clinical development program, this should be considered as missing information and/or a potential risk. This information should be also reflected in the safety specification and pharmacovigilance plan. Whether it is included as a safety concern will depend upon the clinical relevance of possible effects;

- Patients of different racial and/or ethnic origins. The experience of drug use in patients with different racial and/or ethnic origins should be considered including its effects on efficacy, safety, and pharmacokinetics in the target populations. If there is a possibility that efficacy of a medicinal drug may be affected by differences in racial or ethnic origins, assessment should be

given to carry out post-authorization studies of efficacy.

*6.2.5.2.5. RMP module SV “Post-authorization experience”.*

The purpose of this RMP module is to provide information on the number of patients who were prescribed with a medicinal drug in post-authorization period; peculiarities of use in post-authorization practice including use in special patient groups mentioned in RMP module SIV; the number of patients included into observational studies/trials during that safety data was collected and regulatory measures were taken to bring medicinal drug safety information into compliance with available data.

*6.2.5.2.5.1. RMP module SV, section “Regulatory measures and actions taken by MAH related to medicinal drug safety”*

This sub-section of the module lists all regulatory actions (including those initiated by the MAH) in any market, taken in relation to revealed safety concerns for a medicinal drug. This list should include the enumeration and description of the regulatory actions taken with the specification of a country and date. When the RMP is updated, this part should contain description of actions taken since the last submission of the RMP with brief description of the reasons for their implementation.

*6.2.5.2.5.2. RMP module SV, section “Non-study results of post-authorization use”.*

According to the results of marketing of the medicinal drug in various markets, the MAH should provide cumulative data on patients exposed in post-marketing period. Where possible, the information should be stratified by relevant variables which may include age, sex, indication, dose and geographic region. Depending upon the medicinal drug, other variables may be relevant (e.g. number of vaccination courses, route of administration or duration of treatment). It is necessary to make a quantitative and differentiated assessment of impact with the use of the valid method of calculation based on the specialties of use and target populations. The performance of calculation based on the quantity of a medicinal drug sold in a weight/quantitative measurement and correlation with an average recommended dose is possible only if the medicinal drug is always used at one dose level for a fixed course of use/prescription. This approach is not applicable with most medicinal drugs since their dose level and course of use are not fixed as a rule.

If the medicinal drugs have different routes of administration, the calculation of exposure should be done separately, where possible. Competent authorities of Member States of the member states may request additional stratification of exposure data, (e.g. exposure data in different age groups or within different approved indications). However, if the medicinal drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, an MAH should initially provide such data where possible.

*6.2.5.2.5.3. RMP module SV, section “Results of post-authorization use in patient groups not studied in clinical studies/trials”*

If there was post-authorization use of the medicinal drug in the special patient groups identified in RMP module SIV as having no or limited exposure, estimation of the number of patients exposed and the method of calculation should be provided whether or not the use is on- or off-label. For pediatric use, the reference should be made to RMP module SVI, section “Specific aspects of pediatric use”. Information in the safety profile of the medicinal drug for these specific patient groups, as compared with the rest of the target population, should also be provided. In this section any information regarding possible change in benefit profile (efficacy profile) in a special patient group should be provided. Any special patient groups found to be at an increased or decreased risk in relation to a particular aspect of safety profile should be discussed within specific risk assessment in RMP module SVI, but reference should be made in this section as to risks and patient groups affected.

*6.2.5.2.5.4. RMP module SV, section “On-label and actual use”*

Updates to the safety specification should include certain references to how an actual use in the medical practice differed from the predicted one in RMP module SVII and from the approved indication(s) and contraindication(s) for use (off-label use). The section includes information obtained from the drug use studies (or as a result of other observational studies which included the studies of indications for use of the medicinal drug) including the drug use studies which were conducted on request of competent authorities of Member States of the member states for the purposes other than risk management.

Off-label use includes among other issues the use in non-authorized pediatric patients in various age categories and use for indications not specified in SmPC in the cases when such use takes place beyond the clinical study/trial.

When a competent authority of the member state raises concern regarding off-label use, a MAH should attempt to quantitatively assess this use, specifying the data assessment technique employed.

*6.2.5.2.5.5. RMP module SV, section “Use in epidemiological studies”*

The section includes a listing of epidemiological studies which included/include the collection and evaluation of safety data. Information on the study title, study type (e.g. cohort, case-control), population studied (including country and other relevant population descriptors), duration of study, number of patients in each category, disease (if appropriate) and study status (completed or ongoing) should be provided. If a study has been published, a reference should be included in this RMP section, and a corresponding publication provided in RMP annex 7.

*6.2.5.2.6. RMP module SVI “Additional requirements for the safety specification”*

*6.2.5.2.6.1. RMP module SVI, section “Potential risk of overdose”*

Special attention should be given to medicinal drugs where there is an potential risk of overdose, whether intentional or accidental. Examples include medicinal drugs where there is a narrow therapeutic margin or potential for major dose-related toxic reactions, and/or where there is a high risk of intentional overdose in target population (e.g. in depression). If an overdose risk was determined as a safety concern, additional measures are proposed for this safety aspect in the set of appropriate risk minimization measures proposed in RMP module V.

*6.2.5.2.6.2. RMP module SVI, section “Potential risk of transmission of infectious agents”*

The MAH should assess the potential risk of transmission of infectious agents. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential risk of transmission of live virus should be considered.

*6.2.5.2.6.3. RMP module SVI, section “Potential risk of abuse and illegal use”*

The assessment of potential risk of abuse and illegal use should be made in the section. If appropriate, the means of limiting such activity, e.g. by the use of colorants and/or flavorings in the dosage form, limited pack size and controlled distribution should be discussed in RMP.

*6.2.5.2.6.4. RMP module SVI, section “Potential risk of medication errors in prescription/ administration of medicinal drugs”*

The MAH should consider routinely the possibility of medication errors in the prescription or administration of medicinal drugs. In particular, they should assess, prior to marketing of a medicinal drug, common sources of medication errors in its prescription/administration. During the development and design phase of a medicinal drug for marketing, the applicant needs to take into account potential reasons for administration errors. The following should be considered: name, presentation (e.g. size, shape and coloring of the pharmaceutical form and package), information in SmPC (e.g. regarding reconstitution, parenteral route of administration, dose calculation) and labelling. The guideline on the readability of the label and information for patient should be followed. If use of a medicinal drug has potential risk of serious harm when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly reasonable when it is common medical practice to administer the medicinal drug at the same time as other medicinal drugs given by a hazardous route. In this situation, prescription errors should be included as a safety concern.

The sufficiency of visual (or physical) differentiation between strengths of the same medicinal drug and between other medicinal drugs commonly administered or taken at the same time should be assessed. In case if there are other medicinal drugs containing the same

active substance on the market with formulations which are not proven to be bioequivalent, measures to avoid medication errors and to minimize risks should be proposed.

When a medicinal drug is planned to be used by a visually impaired population group, special consideration should be given to the potential for medication error during administration of a medicinal drug that should be considered as a safety concern during risk determination.

Assessment should be given to risk and preventive actions of accidental ingestion or other unintended use by children.

Administration errors identified during drug development including clinical studies/trials should be considered, and information on the errors, their potential causes and remedies given. Where applicable an indication should be given of how these have been taken into account in the final stages of the medicinal drug design.

If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of medication errors, this topic should be discussed in the updated RMP and ways of minimizing the errors proposed.

If the formulation or strength of a medicinal drug is being changed, risk of administration errors should be included as a safety concern and the measures that the MAH will put in place to reduce confusion between old and new medicinal drug should be discussed in the RMP. It may be appropriate to assess risk minimization activities in relation to changes to the presentation, package size, route of administration or other characteristics of the released medicinal drug.

If the medicinal drug is to be administered with a medical device (integrated or not), consideration should be given to all safety concerns which could represent a risk to the patient (medical device malfunctions).

#### *6.2.5.2.6.5. RMP module SVI, section “Specific aspects of pediatric use”*

This section deals with aspects of pediatric use of medicinal drugs not covered in RMP module SIV.

a) Issues identified in a pediatric study plan. Any recommendations for long term follow up of safety and efficacy during use in pediatric population should be detailed here. If this aspect is no longer considered as a subject of safety concern, this should be explained and justified correspondingly.

Proposals for specific long term pediatric studies/trials should be considered at the time of application for a pediatric indication and if felt not to be necessary, justification should be provided;

b) Potential for pediatric off-label use. Risk of a drug off-label use in the pediatric population or some part of it should be assessed in the case when nosology which is an

authorized indication for use of a medicinal drug also occurs in a pediatric population but this medicinal drug is not authorized for use in the latter. Any potential actual use should be discussed in section “Post-authorization experience” (as indicated in section 6.2.5.2. of this document) and in RMP module SV, section “Results of post-authorization use in patient groups not studied in clinical studies/trials” (as indicated in section 6.2.5.3. of this document).

*6.2.5.2.6.6. RMP module SVI, section “Predicted post-authorization use”*

For pre-authorization RMP or on submission of an application for the introduction of significant changes into indications for medical use an MAH should submit a detailed information on the predicted use, assumed use of a medicinal drug by patients as time passed, the status of a medicinal drug in the therapeutic arsenal.

It is necessary to evaluate the potential for the off-label use of a medicinal drug.

*6.2.5.2.7. RMP module SVII “Identified and potential risks”.*

This RMP module provides information on the important identified and potential risks associated with use of the medicinal drug including information on identified and potential adverse reactions, identified and potential interactions with other medicinal drugs, foods and other substances, and pharmacological class effects.

*6.2.5.2.7.1. RMP module SVII, section “Newly identified risks”*

Safety concerns identified since the last submission of the RMP should be listed here and assessed in further details in the appropriate section of RMP module SVII. The causal factor of the safety concern should be stated in the section, whether this risk aspect is an important identified or important potential risk; justification on possible necessary measures of risk minimization or new special studies/trials for this risk aspect should be given.

*6.2.5.2.7.2. RMP module SVII, section “Details of important identified and potential risks”.*

The section contains details of the most important identified and potential risks. This section should be concise and should not be a data sampling of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents of section “Adverse reactions” of SmPC.

The definition of an important risk depends on several factors including the impact on an individual patient, the seriousness of the risk and the impact on public health. Any risk which is/is likely to be included in the contraindications or warnings and precautions section of the SmPC should be included in this section. The interactions of important clinical significance and important pharmacological class effects should also be included into this section. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the studied population group, affect the quality of the

patient's life, and which could lead to serious consequences if untreated (e.g. severe nausea and vomiting connected with chemotherapy or other drug therapy) should also be considered for inclusion to this section.

For some medicinal drugs, risks of disposal of the used medicinal drug (e.g. transdermal patches) should be reviewed. There may also be occasions where there is an environmental concern over medicinal drug disposal because of known harmful effects on the environment (e.g. substances which are particularly hazardous to aquatic wildlife and which should not be disposed of in landfill sites).

Presentation of risk data should include the following detailed information:

- Frequency;
- Public health impact (severity and seriousness/reversibility/outcomes);
- Impact on the individual patient (effect on quality of life);
- Risk factors (including factors related to a patient, dose, at risk period, additive or synergistic factors);
- Preventability (i.e. predictability, possibility of prevention of occurrence or possibility of detection at an early stage);
- Potential mechanism of occurrence;
- Evidence source(s) and strength of the evidence.

The frequency of important identified risks should be expressed taking into account the confidence and the source of the safety data. The frequency should not be calculated based on the number of spontaneous reports as this method does not permit to assess the frequency parameter with the required level of confidence. When an accurate frequency is needed for an important identified risk, this should always be based on systematic studies (e.g. clinical studies/trials or epidemiological studies) in which both the number of patients exposed to the medicinal drug and the number of patients who experienced the respective identified risk are known.

It should be stated clearly which frequency parameter is being used, the units of the denominator should be determined (e.g. number of patients or in patient-days or equivalent units (courses of treatment, prescriptions, etc.)). Confidence intervals should also be provided. When using the patient-time measurement units, the underlying assumption is that the hazard function must be nearly constant over the follow-up time. Otherwise it should be split into relevant categories where the assumption of constancy holds. This may be particularly important if treatment duration is a risk factor. Where appropriate, the period of major risk should be identified. Identified risk incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess of incidence rate compared to a specified comparator group should be given. Data on time to occurrence of adverse events should be summarized using survival techniques. Cumulative hazard functions may also be used to represent the cumulative probability of occurrence of adverse reactions.

For potential risks, the background incidence/prevalence in the target population(s) should be provided.

For RMPs involving single medicinal drugs, risks which relate specifically to an indication or formulation can usually be handled as individual safety concerns (e.g. accidental IV administration could be a safety concern in a single medicinal drug with both oral and subcutaneous forms).

For RMPs covering multiple medicinal drugs where there may be significant differences in the identified and potential risks for different medicinal drugs, it may be appropriate to categorize the risks to make it clearer which risk relates to which medicinal drug. Headings which could be considered include:

a) Risks relating to the active substance. This would include important identified or potential risks which are common to all formulations of medicinal drugs, routes of administration and target population groups. It is likely that most risks will fall into this category for the majority of medicinal drugs;

b) Risks related to a specific formulation or route of administration. Examples might include an RMP with two medicinal drugs (e.g. one a depot intramuscular formulation and the other an oral formulation). Additional concerns relating to accidental intravenous administration clearly would not be applicable to the oral medicinal drugs;

c) Risks relating to a specific target population. The pediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a medicinal drug intended solely for adult patients;

d) Risks associated with switch to non-prescription status.

*6.2.5.2.7.3. RMP module SVII, section "Identified and potential interactions including food-drug and drug-drug interactions"*

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatment regimens for the approved indications for use, but also in relation to commonly used medicinal drugs in the target population. For each, the available data and evidence base supporting the interaction and possible mechanism should be summarized. The potential health risks posed for the different indications and in the different population groups should be assessed. Interactions which are important clinically should be



included in RMP module of identified and potential risks.

*6.2.5.2.7.4. RMP module SVII, section “Pharmacological class effects”*

The section gives the characteristics and assessments of important risks common to the pharmacological class. The discussion concerns the correlation of the frequency of drug-related adverse reactions with the frequency seen with other members of the same pharmacological class.

If there is evidence that a risk, which is common to other members of the pharmacological class, is not thought to be a safety concern in relation to the medicinal drug, and consequently it is not included into the list of identified and potential risks, the evidence supporting this, should be provided in the section.

*6.2.5.2.8. RMP module SVIII “Summary of the safety concerns”*

The section gives a summary of the safety concerns which are classified as:

- a) Important identified risk;
- b) Important potential risk;
- c) Important missing information.

For RMPs covering multiple medicinal drugs it may be appropriate to subdivide the summary of safety concerns under specific headings (similar to the presentation of risks in RMP module SVII) and the following approach to subdivision could be used:

- Safety concerns relating to the active substance;
- Safety concerns related to a specific formulation or route of administration;
- Safety concerns relating to the target population;
- Safety concerns associated with switch to non-prescription status.

*6.2.5.3. RMP Part III “Pharmacovigilance plan”*

The purpose of the pharmacovigilance plan is to determine how the MAH plans to identify and/or characterize the risks identified in the safety requirements. Pharmacovigilance plan provides a structured plan for:

- The identification of new safety concerns;
- Further characterization of known safety concerns including elucidation of risk factors;
- The investigation of whether a potential safety concern is real or not;
- How important missing information will be sought.

The pharmacovigilance plan should be based on the safety concerns summarized in RMP Part II module SVIII "Safety specification".

Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities. For each safety concern, the MAH should list its planned pharmacovigilance activities. Pharmacovigilance plans should be proportionate to the

risks of the medicinal drug. If routine pharmacovigilance activities are reasonably considered sufficient for post-authorization safety monitoring, without the need for additional actions (e.g. safety studies) “routine pharmacovigilance” should be entered against the safety concern.

*6.2.5.3.1. RMP part III, section “Routine pharmacovigilance activities”*

Routine pharmacovigilance is the set of activities which an MAH regularly conducts to fulfill the legal requirements for pharmacovigilance of the member states. The pharmacovigilance system master file contains details of the systems and processes each MAH has in place to achieve this purpose. These details are not required to be submitted in the RMP.

A competent authority of a Member State may make recommendations to an MAH for change in specific activities related to the collection, collation, assessment and submission of information on adverse reactions obtained in the process of spontaneous reporting. In this case in this section an MAH will give notes on the changes in the routine pharmacological activity introduced on the recommendation of the competent authority of a Member State.

Where a MAH is requested, or plans to use, specific adverse reaction follow-up questionnaires to obtain structured information on reported adverse reactions of special interest, copies of these forms should be provided in RMP annex 6. Use of specific questionnaires as a follow-up to a reported suspected adverse reactions is considered to be routine pharmacovigilance.

*6.2.5.3.2. RMP part III, section “Additional pharmacovigilance activities”*

MAHs should consider the situations when additional pharmacovigilance activities are needed because of the impossibility to reach the proper assessment/investigation of risk with routine pharmacovigilance methods.

The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification whether the studies are to identify and characterize risks, or to assess the effectiveness of risk minimization activities. The MAH should include all studies/trials designed to address/assess the safety concerns, and also studies/trials which may give useful safety information, although the security concerns assesses within the RMP may be not included into the priorities of the study. This includes post-authorization safety studies, pharmacoepidemiology studies, pharmacokinetic studies, clinical studies/trials or further pre-clinical work. The appropriate international agreements and government regulations of EAEU should be followed in the conduct of these studies/trials. Protocols for studies/trials in the pharmacovigilance plan and synopses of results of study/trial reports conducted within additional pharmacovigilance activities should be provided in the RMP annexes.

The impact of the new data on the risk-benefit balance of the medicinal drug should be carefully assessed and the safety specification, pharmacovigilance plan and risk minimization measures updated accordingly with regard to safety data obtained.

*6.2.5.3.2.1. Particular situations with post authorization safety studies.*

The studies of the risk minimization measures effectiveness should be included into the pharmacovigilance plan together with particular safety factors and detailed in the risk minimization plan. They should contain the following main aspects including but not limited to:

- Drug utilization studies can be conducted according the request of member states competent authorities of Member States to monitor medicinal drug use in the territory, often in relation to the evaluation of reimbursement strategy a state offers to population for expenses on medicinal drugs. This type of investigations is not designed immediately for studying safety aspects of medicinal drugs, but it may give useful information whether the risk minimization measures are effective or not, and on the demography of target population groups;

- Joint studies. If a safety concern applies to more than one medicinal drug (or one active substance is per several MAHs) the competent authority of a Member State should encourage the MAHs concerned to conduct a joint PASS (a post-authorization safety study). The conduct of joint studies may also be necessary where there are limited patients (rare diseases) or adverse reactions are rare. The competent authority of a member state should facilitate the agreement of the concerned MAHs in developing a single protocol for the PASS and conducting the joint study. If, within a reasonable period of time, as determined by the competent authority of a Member State, the concerned MAHs have failed to agree on a common protocol, the competent authority of a Member State may impose a PASS and define either a common core protocol or key elements within a protocol which the MAHs concerned will have to implement within a timescale laid down;

- Registry is a type of prospective non-interventional cohort studies. It is recommended that the registry should include a comparator group so a disease registry will usually be more suitable than a registry confined to a specific medicinal drug. The protocol for the registry will allow all patients who are prescribed the relevant medicinal drugs or who have the same disease, as appropriate, to be entered in the registry.

*6.2.5.3.3. RMP part III, section “Action plans for safety concerns with additional pharmacovigilance requirements”*

For safety concerns with additional pharmacovigilance activities only, the action plan for each safety concern should be presented according to the following structure:

- Safety concern;
- Objective of proposed action(s);

- Proposed action(s);
- Main stages of assessment and reporting.

One of the constituent measures proposed for each safety concern will always be “routine pharmacovigilance”. Besides listing additional actions in the item “Proposed action(s)” RMP annex 5 should include the protocols (a draft or other document) for the conduct of any studies.

*6.2.5.3.4. RMP part III, section “Summary table of additional pharmacovigilance activities”*

In this section there should be given a summary table of all additional pharmacovigilance activities including the expected dates when results will be available.

*6.2.5.4. RMP part IV “Plans for post-authorization efficacy studies”.*

The requirement for post-authorization safety studies refers solely to the current indication(s) and not to studies investigating additional non-approved indications. Safety studies being special obligations and/or a condition for obtaining a certificate of the state registration should also be included in this part of the RMP.

*6.2.5.4.1. RMP part IV, section “Presentation of efficacy data”.*

As background to any proposed efficacy studies, and to provide supporting data on inclusion to RMP, there should be a summary of the proven efficacy of the medicinal drug and information on the clinical studies/trials and endpoints on which it was based. The robustness of the endpoints on which the efficacy evaluation is based should be assessed.

The section includes a brief evaluation of the need for further post-authorization efficacy studies of the following aspects:

- Applicability of the efficacy data to all patients in the target population;
- Factors which might affect the efficacy of the medicinal drug in everyday medical practice;
- Variability in therapeutic benefits in sub populations.

A summary table showing an overview of the planned studies/trials together with timelines and milestones should be provided here. The draft protocols for these clinical studies/trials are included in RMP annex 7.

*6.2.5.5. RMP Part V “Risk minimization measures”*

On the basis of the safety specification, an MAH should assess what risk minimization activities are needed for each safety concern. The risk minimization plan should provide details of the risk minimization measures which will be taken to reduce the risks associated with each specified safety concern. The proposed risk minimization measures for each safety concern may include more than one risk minimization measure.

Risk minimization measures may consist of routine risk minimization measures and

additional risk minimization measures. All risk minimization measures should have a clearly specified objective.

#### *6.2.5.4.1. RMP Part V “Routine risk minimization measures”*

Routine risk minimization activities include the measures/actions which are carried out in relation to every medicinal drug. Routine measures cover:

- SmPC;
- the labelling;
- the package leaflet/patient information leaflet;
- the package size(s);
- the legal status of the medicinal drug.

The SmPC and the package leaflet/patient information leaflet are important tools for risk minimization as they constitute a controlled and standardized format for informing healthcare and pharmaceutical professionals and patients about the medicinal drug.

Package size which allows to limit the number of dosage units of prescribed medicinal drug is another routine risk minimization measure. Controlling the number of dosage units should mean that patients will need to see a healthcare professional at shorter intervals: optimizing the control over a patient's condition and reducing the length of time a patient is without review. The issue of small pack sizes (in special cases - in one dosage unit) can also be useful, especially if overdose is thought to be a major risk.

Regulatory status of the medicinal drug controlling the conditions under which a medicinal drug may be made available can reduce the risks associated with its use or misuse. This can be achieved by controlling the conditions under which a medicinal drug may be prescribed, or the conditions under which a patient may receive a medicinal drug. When a marketing authorization is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the medicinal drug, including the conditions under which a medicinal drug may be made available to patients. It is commonly referred to as the “regulatory status” of a medicinal drug. This status includes information on whether or not the medicinal drug is subject to medicinal prescription. It may also restrict the places where the medicinal drug can be administered (e.g. in a hospital only). For medicinal drugs only available on prescription, additional conditions should be imposed by classifying medicinal drugs into those available only upon a special medical prescription.

Most of safety concerns may be adequately addressed by routine risk minimization activities. However, for some risks, routine risk minimization activities will not be sufficient and additional risk minimization activities will be necessary.

#### *6.2.5.5.2. RMP part V, section “Additional risk minimization activities”*

Additional risk minimization activities are those risk minimization measures (which are not the routine risk minimization activities listed above) should only be suggested when routine activities are insufficient for the safe and effective use of the medicinal drug. A number of additional risk minimization methods is based on the means of reporting which are beyond the SmPC and the package leaflet/patient information leaflet.

For additional risk minimization measures a detailed description and a justification of the necessity to fulfill them are given. This section should include only those measures which are connected with the safe and efficient use; they should be also science based, developed and provided by suitably qualified people.

Additional risk minimization activities will become, once agreed by the competent authority of the member states, the conditions of the marketing authorization. Where appropriate, full details of additional risk minimization activities (including draft educational materials) should be provided in RMP annex 9.

Educational materials should be non-promotional. The competent authorities of Member States of the member states execute the agreement and approval of educational materials which are developed under the risk minimization plan.

For the medicinal drugs containing the same active substance it is recommended to develop educational materials and materials for patients with as similar as possible format and content.

#### *6.2.5.5.3. Format of risk minimization plan(s)*

For each safety concern specified in the safety specification the following information should be provided:

- Safety concern description;
- Objectives of the proposed activity(-ies);
- Routine risk minimization activities;
- Additional risk minimization activities (if any), individual tasks and justification of need;
- How the effectiveness of risk minimization activities will be evaluated in terms of attainment of their stated objectives;
- What the target is for risk minimization, i.e. what are the criteria for judging success;
- Main stages of assessment and reporting.

For routine risk minimization activities, the proposed text for the SmPC and the package leaflet/patient information leaflet should be provided along with details of any other routine risk minimization activities proposed for safety concerns.

#### *6.2.5.5.4. Updating risk minimization plan*

On updating a RMP should include the assessment of the performed routine and/or additional risk minimization measures. This section should also include the results of the official assessment of risk minimization measures. As part of this critical evaluation, the MAH should identify and assess factors contributing either to the achieving objectives on risk minimization or low effectiveness of risk minimization activities. A comment should be given on whether additional and/or different risk minimization activities are needed for each safety concern.

*6.2.5.5.5. RMP part V, section “Evaluation of the effectiveness of risk minimization activities”*

Risk minimization measures are actions intended to prevent the occurrence of adverse reactions, or to reduce the frequency of occurrence or the severity of adverse reactions and minimization of adverse effects to a patient should the adverse reactions occur. The effectiveness of risk minimization activities in delivering these objectives needs to be evaluated throughout the lifecycle of a medicinal drug to ensure that the burden of adverse reactions are minimized and hence the overall risk-benefit balance is optimized.

If a particular risk minimization strategy proves ineffective, then alternative activities need to be developed and put in place. In certain cases it may be judged that risk minimization activities cannot control the risks to the extent possible to ensure a positive risk-benefit balance and that the medicinal drug needs to be withdrawn either from the market or restricted to those patients subgroup only where the benefits outweigh the risks.

*6.2.5.6. RMP part VI “Summary of risk minimization plan”*

A summary of the RMP for each medicinal drug shall be made publically available. The summary must include key elements of the RMP with a specific focus on risk minimization activities. With regard to the safety specification of the medicinal drug concerned, it should contain important information on identified and potential risks as well as missing information.

The summary of the RMP part VI should contain the following information based on RMP modules SI, SVIII and RMP parts IV and V:

- Overview of disease epidemiology;
- Summary of benefit/efficacy data;
- Missing information on benefit/efficacy data;
- Summary of the safety concerns;
- Tables;
- Summary of risk minimization activities by each safety concern;

- Post-authorization development plan (in relation to safety and efficacy) which includes a detailed description and explanation of all measures that are conditions for obtaining a marketing authorization.

*6.2.5.6.1. RMP part VI, section “Overview of disease epidemiology and the summary of expected benefits”*

The MAH should summarize the epidemiology data on the diseases/conditions, the medicinal drug is indicated for, as presented in details in RMP part II module SI. This information is given as plain facts and in language appropriate to the target population. If the medicinal drug is a diagnostic drug or is used for anesthesia or has similar indications not associated with a particular disease/condition then this section of the overview may be omitted.

*6.2.5.6.2. RMP part VI, section “Summary of safety concerns (in common language)”*

This section should describe in brief safety concerns in the suitable language for patients and caregivers. It should include the frequency and severity of safety concerns. For important potential risks the reasons why the risks arose should be explained together with possible uncertainties (e.g. the risk occurs in other medicinal drugs in the same class but was not seen in the clinical studies when prescribing this medicinal drug). For important missing information it should be stated how it may impact the target population and the recommendations (e.g. contraindication, use with caution etc.).

*6.2.5.6.3. RMP part VI, section “Summary table of risk minimization activities by safety concerns”*

This section should include safety concerns and a summary of risk minimization activities proposed for each safety concern. If more than one risk minimization plan (RMP Part V) is available, for each plan there should be a separate table.

*6.2.5.6.4. RMP part VI, section “Planned post-authorization activity on the assessment of efficacy and pharmacovigilance development”*

Data should be presented in the form of a table showing the planned activities in terms of efficacy studies and the further investigation of safety concerns. The objective is to present the review of the planned post-authorization development of a medicinal drug in terms of the assessment of efficacy and pharmacovigilance, and the consideration of the main stages in relation to each study or activity. This table should combine the tables from sections 6.2.5.3.4. and 6.2.5.4.1. Each row of the table should include the cause of the study, name of the study and a brief description of the study, timelines and main stages of the study.

*6.2.5.6.5. RMP part VI, section “Summary of changes to the risk management plan”*

This section should include a table which provides a listing of all significant changes to the RMP in chronological order. This should include, for example, the date of the RMP when



new safety concerns were added or existing ones removed, dates when new safety studies were added or finished, and a brief summary of changes to the plan of risk minimization activities and the associated dates these changes were agreed.

#### *6.2.5.7. RMP part VII “Annexes to the risk management plan”*

The RMP should contain the annexes listed below.

RMP annex 1: Current (or proposed if a medicinal drug is not authorized) version of the SmPC and package leaflet/patient information leaflet;

RMP annex 2: Synopsis of on-going and completed clinical studies/trials;

RMP annex 3: Synopsis of on-going and completed pharmacoepidemiological studies/trials;

RMP annex 4: Protocols for proposed and on-going studies in RMP part III;

RMP annex 5: Specific adverse event follow-up forms;

RMP annex 6: Protocols for proposed and on-going studies in RMP part IV;

RMP annex 7: New available reports on studies/trials;

RMP annex 8: Details of proposed additional risk minimization activities (if applicable);

RMP annex 9: Other supporting data (including referenced material).

#### *6.2.6. The relationship between the risk management plan and the periodic safety update report*

The primary post-authorization pharmacovigilance documents will be the RMP and the periodic safety update report (PSUR). The main purpose of the PSUR is integrated, post-authorization risk-benefit assessment whilst that of the RMP is pre- and post-authorization risk-benefit management and planning. As such the two documents are complementary. The PSUR examines the overall safety profile as part of an integrated risk-benefit evaluation of the medicinal drug at set time periods and as such will consider the overall risk-benefit balance of the medicinal drug (and a much wider range of suspected adverse reactions). It is anticipated that only a small proportion of these risks would be classified as important identified or important potential risks and become a safety concern discussed within the RMP.

When a PSUR and a RMP are to be submitted together, the RMP should reflect the conclusions on safety and efficacy profile provided in PSUR. For example if a new signal is discussed in the PSUR and the PSUR concludes that this is an important identified or important potential risk, this risk should be included as a safety concern in the updated RMP submitted with the PSUR. The pharmacovigilance plan and the risk minimization plan should be updated to reflect the MAH's proposals to further investigate the safety concern and minimize the relevant risk.

#### *6.2.7. Principles for assessment of risk management plans*

The main issues which need to be considered when preparing or reviewing a risk

management plan for a medicinal drug should include analysis of information performed taking into account profile of the document of Pharmacovigilance system appropriate or analysis of pharmacovigilance activities.

*6.2.7.1. Safety specification is analyzed according the following questions:*

- Have all appropriate parts of the safety specification been included?
- Have all appropriate data been reviewed when compiling the safety specification, i.e. are there important (outstanding) issues from other sections of the dossier which have not been discussed in the safety specification?
  - If a part of the target population has not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
  - What are the limitations of the safety database and what reassurance does it provide regarding accuracy of assessment of the safety profile of the medicinal drug?
  - Does the safety specification include specific risks, e.g. off-label use, misuse and abuse, medication error, transmission of infectious disease, etc?
  - Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and important missing information) with the medicinal drugs concerned?
    - If a generic medicinal drug, have all safety concerns specified for the reference medicinal drug been included in the safety specification?
    - Does its place in the therapeutic arsenal as described concur with the intended indication and current medical practice?

*6.2.7.2. Pharmacovigilance plan is analyzed according the following questions:*

- Are all safety concerns from the safety specification covered in the pharmacovigilance plan?
- Are routine pharmacovigilance activities adequate (as it is given in the description of the pharmacovigilance system) or are additional pharmacovigilance activities necessary?
- Are the activities in the pharmacovigilance plan clearly defined and described and suitable for identifying or characterizing risks or providing missing information?
- Does the RMP include appropriate and adequate proposals to monitor medication errors in the use of a medicinal drug?
  - Are the proposed additional studies/trials necessary and/or useful?
  - When draft protocols are provided, are the proposed studies in the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?

- Are appropriate timelines and main stages defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?

*6.2.7.3. Plans for post-authorization safety studies are analyzed according the following questions:*

- Does the description of the efficacy of the medicinal drug and studies and endpoints it was based on conform to the contents of the dossier?

- Are any of the proposed studies of an advertising nature (i.e. a study that does not put a scientific issue as its primary aim and is designed to increase demand in a medicinal drug)?

- How are data on efficacy reliable and is there necessity in a request for further study of efficacy as a condition for obtaining a marketing authorization?

*6.2.7.4. Risk minimization measures are analyzed according the following questions:*

- Does the drug information adequately reflect all important identified risks and important missing information?

- Are any potential risks sufficiently relevant to the safe and effective use of the medicinal drug that information about them should be included in the drug information?

- Is the proposed wording about the risks and their revealing appropriate and in line with relevant information and recommendations given in the SmPC?

- Has the MAH considered ways to reduce the risk of medication errors during the use of a medicinal drug?

- Has this been included into appropriate drug information, measures (including device design where appropriate) and the package design?

- Are proposed risk minimization activities appropriate and sufficient?

- Have additional risk minimization activities been suggested and if so, are they risk proportionate and adequately justified?

- Are the methodologies for measuring and assessing the effectiveness of risk minimization activities well described and appropriate?

- Have criteria for evaluating the effectiveness of additional risk minimization activities been defined a priori?

*6.2.7.5. The following questions are analyzed when an update is being assessed:*

- Has new data been incorporated into the safety specification?

- Have appropriate changes been made to the pharmacovigilance plan (if necessary in the light of new data)?

- How effective were the incorporated risk minimization measures?

- Have appropriate changes to risk minimization measures been proposed if necessary?

- Does the new data suggest that a formal evaluation of the risk-benefit balance (if not already done in a PSUR) is needed?

### ***6.2.8. Quality systems and record management***

Although many experts may be involved in writing the RMP, the final responsibility for its quality, accuracy and scientific integrity lies on the qualified persons responsible for pharmacovigilance (QPPV) in the member states. The MAH is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in Module 2 of the guidance. The MAH should provide the control and documentation of the procedure for submission RMs to competent authorities of Member States of the member states with the specification of submission dates and all the significant changes between each version of the RMP. These records, the RMPs and any documents relating to information within the RMP may be subject to inspection by appropriately qualified pharmacovigilance inspectors.

## **6.3. Requirements to submission**

### ***6.3.1. Situations when a risk management plan should be submitted***

An RMP or its update, as applicable, may need to be submitted at any time during a life-cycle of the medicinal drug.

6.3.1.1. When a primary application for the marketing authorization of a medicinal drug is filed, the RMP is submitted in the following cases:

- If a marketing authorization application concerns a medicinal drug containing an active substance that was not earlier registered in an EAEU member state;
- If a marketing authorization application concerns a medicinal drug containing a combination of active substances that were not earlier registered in an EAEU member state;
- If a marketing authorization application concerns a medicinal drug of biological origin;

A competent authority of a Member State may require a RMP to be submitted when a marketing authorization application is filed in other cases, when the provision of the use of a medicinal drug, when benefit exceeds risk, demands the introduction of additional pharmacovigilance measures or risk minimization measures.

6.3.1.2. A competent authority of a Member State may require an RMP to be submitted in the following cases:

- With an application involving significant changes to an existing marketing authorization, scope of use, aspects of manufacturing process (e.g. new formulation, new route of administration, new manufacturing process of a biotechnological medicinal drugs, pediatric indications, other significant changes in indication);
- When there is a safety concern affecting the risk-benefit balance;

- At the time of the renewal of the marketing authorization if the medicinal drug has an existing RMP.

#### 6.3.1.1. Requirements in specific situations

Normally all parts of an RMP should be submitted. However, in certain circumstances as detailed below, in line with the concept of proportionality, certain parts or modules may be omitted, unless otherwise requested by the competent authority of a member state. However, any safety concerns identified in a reference medicinal drug in a module which is omitted from the RMP should be included in RMP module CVIII unless clearly no longer relevant.

#### **Initial application for registration of generic medicinal drugs**

In the case of initial application for registration of new generics for which an RMP is submitted regarding brand name medicinal drugs, the modules SII-SV of safety specification may be omitted. RMP module SVI of safety specification should be based on the safety concerns specified for the brand name medicinal drug unless the generic differs significantly in properties which could relate to safety profile, or unless requested otherwise by the competent authority of the Member State. Provided the brand name medicinal drug does not have any additional pharmacovigilance activities or efficacy studies imposed as a condition of the marketing authorization, RMP parts III and IV and the section of the planned post-authorization development in RMP part VI may be omitted.

For updates to the RMP, RMP module SV should be included.

Applications for inclusion of a new indication for medical use of a medicinal drug authorized in the territory of EAEU member states for last 10 years.

While application for the inclusion of a new indication of a medicinal drug authorized in the territory of EAEU member states for last 10 years, the clinical studies/trials data related to the approved indications may be omitted from RMP module SIII of safety specification, and RMP module SIV of safety specification should include information only in relation to the target population groups under a new indication unless the competent authority of a Member State submits other requirements. However, data from experience of the use of the already authorized medicinal drugs in the special population groups which are the subject of RMP module SIV may be included.

When initial marketing authorization application is filed, requirements to data submitted in RMP modules are given in Table 1.

Table 1. Requirements to data submitted in RMP modules, when new marketing authorization application is filed

Type of a medicinal drug	Part I	Part II									Parts				
		SI	SII	SIII	SIV	SV	SVI	SVIa	SVII	SVIII	III	IV	V	VI	VII
<b>New active substance</b>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>Biosimilar</b>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<b>Generic medicinal drug</b>	+						+	+	+	+	*	*	+	*	+
<b>Fixed combinations</b>	+	+	‡	‡	+	+	+	+	+	+	+	+	+	+	+
<b>Hybrid medicinal drug</b>	+	+	*	*		+	+	+	+	+	+	+	+	+	+

‡ May be omitted under certain circumstances

\* Modified requirement

Initial risk management plan for medicinal drugs marketed in the territory of EAEU member states for 10 years.

Unless otherwise requested by the competent authority of the Member State, MAHs required to submit an initial RMP for medicinal drugs marketed in the member state and may omit modules SIII and SIV of safety specification if the following conditions are met:

- The medicinal drug was placed on the market 10 or more years before the requirement for an RMP is established; and

- The requirement for an RMP is not due to an application for a significant change to an existing marketing authorization, scope of use, aspects of the manufacturing process. If this condition cannot be met, clinical study/trial data relating to this change should be supplied in RMP module SIII of safety specification, and RMP module SIV of safety specification may be omitted. Discussion of the existing post-authorization data and its applicability to the target patient groups should be extensively discussed in RMP module SV of safety specification.

### ***6.3.2. Updates to the risk management plan***

If an RMP has previously been submitted by the MAH during registration procedure for the active substance, any following submissions shall be in the form of an update unless requested otherwise. Each submission of the RMP shall have a distinct version number and shall be dated. This applies whether the entire RMP or only its part or module is being submitted. Versions with changes containing identifying information should be submitted along with a cover letter detailing the changes since the last submitted version.

The timelines for providing updates to the RMP will normally be set during its introduction and as a condition of retaining the regulatory status. These pre-established time frames are deadlines, they do not relieve the MAH of the responsibility for monitoring the safety profile of the medicinal products and the requirement to submit the updated RMP before the scheduled update submission time if a significant change occurs in the estimated

risk-benefit balance of the respective medicinal products included in the RMP.

If no changes have been made in the RMP since the last submission (i.e. a scheduled renewal occurs soon after the procedure completion), the marketing authorization holder may prepare a letter explaining the absence of changes and not submit an RMP update as agreed upon with the competent authority of a Member State.

Unless specified otherwise, when both PSUR and RMP are required for a medicinal drug, routine updates to the RMP should be submitted at the same time as the PSUR.

When the RMP is updated, the risk minimization plan should include an evaluation of efficacy and the results of routine and/or additional risk minimization activities as applicable (in accordance with the subsection 6.2.5.5.4. of this guidance).

### ***6.3.3. Transparency***

The competent authorities of Member States of the EAEU member states shall provide a mutual availability of assessment reports and summaries of RMPs via an appropriate web-portal.

## **7. MANAGEMENT OF ADVERSE DRUG REACTIONS INFORMATION**

### **7.1 Structures and processes**

This section highlights the general principles in relation to the collection, recording, and reporting of suspected adverse reactions associated with medicinal products.

#### ***7.1.1. Collection of adverse reaction reports***

Competent authorities and marketing authorization holders should take appropriate measures in order to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from various unsolicited or solicited sources.

In order to ensure acquisition of sufficient number of the adverse reactions' reports and subsequent scientific evaluation of these reports it is necessary to develop a pharmacovigilance system.

The system should be designed so that it helps to ensure appropriate assessment of the quality of the collected reports (as regards authenticity, legibility, accuracy, consistency), should be verifiable and as complete as possible for their clinical assessment.

The system should also be structured in a way that allows for reports of suspected adverse reactions to be validated in a timely manner and exchanged between competent authorities of Member States and marketing authorization holders within the legal reporting time frame.

##### ***7.1.1.1. Unsolicited reports***

###### ***7.1.1.1.1. Spontaneous reports***

A spontaneous report is an unsolicited communication by a health care professional, patient, or consumer to a competent authority, marketing authorization holder or other organization (for instance, Regional Centre, toxicological) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products. Spontaneous reports do not include reports deriving from a study or any other organized data collection systems.

The source of a suspected adverse reaction is the one which communicated information about the adverse drug reaction case. If information about the same adverse drug reaction is obtained from several sources, such as a health care professional, patient, or consumer, data from all these sources should be included in the "Source" section of the adverse reaction reporting form.

Stimulated reporting that occurs consequent to a "Direct health care professional communication", publications in the press, questioning of health care professionals by representatives of marketing authorization holders, or class action lawsuits should be



considered spontaneous reports as well.

Unsolicited patient or consumer adverse reactions reports should be handled as spontaneous reports irrespective of any subsequent “medical confirmation”.

If a spontaneous adverse event report is received that contains no indication of a causal relationship, this adverse event should be considered an adverse reaction. Therefore, all spontaneous reports received from health care professionals, patients, or consumers should be regarded as suspected adverse reactions basing on the fact that these reports contain source’s assumption on causal relationship. The exception is the reports where the reporter states no association between the adverse event and the use of the suspected medicinal product.

#### *7.1.1.1.2. Adverse reaction reports published in medical literature*

The scientific medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorization holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (for instance, Medline, Excerpta Medica, or Embase) no less frequently than once a week. The marketing authorization holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the monitored medicinal product. In addition, marketing authorization holders should have procedures in place to monitor medical publications in local journals in countries where medicinal products have a marketing authorization, and to bring them to the attention of the company safety department as appropriate.

Reports of suspected adverse reactions from the scientific medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by marketing authorization holders to identify and record reports of adverse reactions associated with the medicinal products, originating from spontaneous reports or reports from non-interventional post-authorization studies.

If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's authors as having at least a possible causal relationship with the identified suspected adverse reaction should be considered by the concerned marketing authorization holder. This requirement also applies to reports published in the scientific medical literature of a country where the marketing authorization holder has received a state registration certificate but has never marketed the medicinal product.

Reports assessed as valid should be submitted to the competent authorities of Member States of Member States in accordance with the current legal requirements. The clock start time

for adverse reaction report submission is the moment when the marketing authorization holder receives information concerning the adverse reaction which meets the requirements for minimum information requiring expedited reporting. One case should be created for each single identifiable patient in the report. Relevant medical information should be provided for assessment. Article references should be considered as the primary sources for the respective adverse reactions.

#### *7.1.1.1.3. Reports from other sources*

If a marketing authorization holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be handled as a spontaneous report. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid adverse reaction report. The same reporting time frames should be applied as for other spontaneous reports.

#### *7.1.1.1.4. Information on suspected adverse reactions from the internet or digital media*

Marketing authorization holders should regularly screen in internet or digital media: websites, web pages, blogs, video blogs, social media, internet forums, chat rooms, health portals under their management or responsibility, for potential reports of suspected adverse reactions. In this context, digital media is considered to be company-sponsored if it is owned, paid for, and / or controlled by the marketing authorization holder. A donation (financial or otherwise) to an organization / site by a medicinal product manufacturer / marketing authorization holder does not constitute ownership, provided that the medicinal product manufacturer / marketing authorization holder does not control the final content of the site. The frequency of the screening should allow for potential valid ICSRs to be reported to the competent authorities of Member States within the appropriate reporting time frame based on the date the information was posted.

Marketing authorization holders may also consider actively monitor special dedicated websites or digital media, such as patient support sites or sites of certain disease groups, to check whether they cover important safety issues that may require reporting in accordance with applicable current requirements. The periodicity of monitoring of these websites or digital media should be determined by the risks associated with the monitored medicinal product.

Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied.

In relation to cases from the internet or digital media, the identifiability of the reporter refers to the check of existence of a real person, that is, it should be possible to verify the contact

details of the reporter (for instance, an e-mail address under a valid format has been provided). The contact details should be used for the purposes of pharmacovigilance only. If the country of the primary source is missing, the country where the information was received, depending on where the monitoring took place, should be used as the primary source country.

If a marketing authorization holder becomes aware of a report of a suspected adverse reaction described in any non-company-sponsored digital medium, the report should be assessed to determine whether it qualifies for expedited reporting.

#### *7.1.1.2. Solicited reports*

Solicited reports of suspected adverse reactions are reports derived from organized data collection systems, which include clinical studies, non-interventional studies, registries, named patient use programmes for unauthorized medicinal products, other patient use programmes for unauthorized medicinal products, compassionate use and disease management programmes, surveys of patients or health care providers, or information gathering on efficacy or patient compliance. Reports of suspected adverse reactions obtained from any of these data collection systems should not be considered spontaneous.

For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they meet the criteria for expedited reporting.

#### *7.1.2. Validation of reports*

*7.1.2.1.* Only valid individual case safety reports qualify for expedited reporting. To meet this requirement, all reports of suspected adverse reactions should be validated before reporting them to the competent authorities of Member States to make sure that the minimum criteria for reporting are included in the reports. These minimum criteria for reporting are:

- an identifiable reporter (primary source), characterized by name, initials, address, or qualification (for instance, physician, pharmacist, other health care professional, patient, consumer or other non-health care professional). A reporter is considered identifiable if the contact details of the reporter are available, so that report verification or follow-up activities can be performed if deemed necessary. All parties providing adverse reaction information, including solicited additional information, should be identifiable. If the reporter does not wish to provide contact details, the adverse reaction report should still be considered as valid if the organization informed on the case is able to confirm it directly with the reporter.

- an identifiable patient characterized by initials, patient identification number, date of birth, age, age group, or gender. The patient identification information should be as complete as possible.

- at least one suspected medicinal product.

- at least one suspected adverse reaction. If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse reaction has been excluded and the receiver (competent authority or marketing authorization holder) agrees with this, the report is not qualified as a valid individual case safety report since the minimum information is incomplete. The report is not also qualified as a valid individual case safety report if it is reported that the patient experienced an unspecified adverse reaction and there is no indication or description provided on the type of adverse reaction experienced.

7.1.2.2. When collecting reports of suspected adverse reactions via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a reporter and a patient.

7.1.2.3. The lack of any of these four elements means that the case is considered incomplete and does not qualify for expedited reporting. Competent authorities of Member States of member-states and marketing authorization holders are expected to exercise due diligence in following up the case to collect the missing data elements. Nevertheless, adverse reaction reports, for which the minimum information is incomplete, should be recorded within the pharmacovigilance system for use in on-going safety evaluation activities.

7.1.2.4. When one party (the competent authority or a marketing authorization holder) is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the report should nevertheless be considered as a valid individual case safety report. All the relevant information necessary for the detection of the duplicate case should be included in the individual case safety report.

7.1.2.5. In the case of post-authorization non-interventional studies, where the investigator and the marketing authorization holder / sponsor disagree on causal relationship between the use of the suspected medicinal product and the adverse reaction expressed by the primary source, the case should not be downgraded to an adverse event of a lower relationship reliability category. The opinions of both, the primary source and the marketing authorization holder / study sponsor, should be recorded in the individual case safety report.

### **7.1.3. *Follow-up of adverse reaction reports***

7.1.3.1. When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the adverse reaction cases.

7.1.3.2. Follow-up methods should be tailored towards optimizing the collection of missing information. Written confirmation of verbal communications should be obtained as much as possible. These standard pharmacovigilance activities should be done in ways that encourage the primary source (reporter) to submit new information relevant for the scientific

evaluation of a particular safety concern.

7.1.3.3. When information is received directly from a patient or consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to obtain consent to contact a nominated health care professional to obtain further follow-up information. When such a case, initially reported by a patient or consumer, has been confirmed (totally or partially) by a health care professional, this information should be accurately described in the individual case safety report.

7.1.3.4. With regard to suspected adverse drug reactions associated with biological medicinal products, the definite identification of the concerned medicinal product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the trade name of the medicinal product and the batch number.

#### **7.1.4. Data management**

7.1.4.1. Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability and in accordance with the requirements of the national data privacy laws. Identifiable personal details of reporting health care professionals (reporters) should be kept in confidence.

7.1.4.2. In order to ensure pharmacovigilance data security and confidentiality, strict access controls should be applied to documents and to databases to authorized personnel only. This security requirement extends to the complete data path. In this aspect, procedures should be implemented to ensure security and non-corruption of data during data transfer.

7.1.4.3. When transfer of pharmacovigilance data occurs within an organization or between organizations, the mechanism should be such that there is confidence that all notifications are received. In that case, a confirmation and / or reconciliation process should be undertaken. Information related to an adverse reaction report may be communicated only between interested individuals, in anonymous format.

7.1.4.4. Electronic data storage should ensure online access.

7.1.4.5. The terminology use procedure should be monitored and validated by means of quality assurance audit, either systematically or as periodic random evaluations. Data entry staff should be instructed in the use of the terminologies, and their proficiency confirmed at regular intervals. Data received from the primary source (reporter) should be treated in an unbiased and unfiltered way and inferences, as well as imputations, should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source or an accurate translation of it. The original verbatim text should be coded using the appropriate terminology.

7.1.4.6. Electronic data storage should allow traceability (audit trail) of all data entered or modified, including the dates and sources of received data, as well as the dates and destinations of transmitted data.

7.1.4.7. Databases should be checked regularly with the aim to identify and handle duplicate adverse reaction reports.

### **7.1.5. *Quality management***

7.1.5.1. Competent authorities of Member States of member-states and marketing authorization holders should create and implement a quality management system to ensure compliance with the necessary quality standards at every stage of adverse reactions documentation, such as data collection, data transfer, data management, data coding and archiving, case validation, case evaluation, case follow-up, and individual case safety reporting. Conformity of stored data with source information and further report assessment should be verified by quality control procedures, which permit for the validation against the original data or images thereof. In this aspect, the source data (for instance, letters, e-mails, records of telephone calls that include details of a reaction) or an image of the source data should be easily accessible.

7.1.5.2. Written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

7.1.5.3. Staff directly performing pharmacovigilance activities, as well as other personnel who may receive or process safety reports (for instance, clinical development, sales, medical information, legal, quality control), should be appropriately trained. This training should cover applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities.

### **7.1.6. *Special situations***

#### **7.1.6.1. *Use of a medicinal product during pregnancy or breastfeeding***

##### **7.1.6.1.1. *Pregnancy***

Reports, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. When an active substance (or one of its metabolites) has a long elimination half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the medicinal product was taken before conception.

Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product. In this context the development and use of standard structured questionnaires is recommended.

Individual cases with an unfavorable outcome associated with a medicinal product following exposure during pregnancy are classified as serious adverse reactions and should be reported urgently, in accordance with applicable legal requirements of member-states.

This particularly refers to the following cases:

- reports of congenital anomalies or developmental delay, in the fetus or the child;
- reports of fetal death and spontaneous abortion;
- reports of suspected adverse reactions in the neonate that are classified as serious.

Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome, should not be reported urgently, since there is no suspected adverse reaction. These reports should, however, be handled along with other adverse drug reaction reports.

However, in certain circumstances, all reports of pregnancy exposure with no suspected reactions may necessitate to be urgently reported. This may be a requirement / condition stipulated in the risk management plan; this is usually the case with medicinal products contraindicated in pregnancy or medicinal products with a special need for surveillance because of a high teratogenic potential (for instance, treatment with medicinal products similar to thalidomide, isotretinoin).

A signal of a possible teratogen effect (for instance, through a cluster of similar abnormal pregnancy outcomes) should be notified immediately to the competent authorities of Member States.

#### *7.1.6.1.2. Breastfeeding*

Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported.

#### *7.1.6.2. Use of a medicinal product in a pediatric or elderly population.*

All reasonable attempts should be made to obtain and submit the age or age group of the patient when a case is reported by a health care professional, patient, or consumer in order to be able to identify potential safety signals specific to a particular population.

If use of a medicinal product is common in patient populations not specified in the approved Summary of Product Characteristics, it is essential that both the competent authorities of Member States of member-states and the marketing authorization holders monitor any

subsequent safety issues and take appropriate measures to address them. Marketing authorization holders and competent authorities of Member States of member-states should encourage preparation and presentation of reports on all suspected adverse drug reactions, even if they occur in population groups not specified in the Summary of Product Characteristics.

*7.1.6.3. Reports of overdose, abuse, misuse, medication error or occupational exposure.*

Reports of overdose, abuse, misuse, medication error, or occupational exposure with no associated adverse reaction should not be reported urgently. They should be considered in the respective periodic safety update reports and risk management plan if applicable. When those reports constitute safety issues impacting on the risk - benefit balance of the medicinal product, they should be notified to the competent authorities of Member States of member-states in accordance with applicable legal requirements.

*7.1.6.4. Lack of therapeutic efficacy*

Reports of lack of therapeutic efficacy should be recorded and followed-up if incomplete. They should not normally be reported urgently, but should be discussed in the periodic safety update report as applicable. However, in certain circumstances, reports of lack of therapeutic efficacy may require to be reported within a 15-day time frame. These cases include lack of therapeutic efficacy associated with the use of a suspected medicinal product administered for the treatment of life-threatening diseases (including life-threatening infectious diseases caused by a susceptible microorganism or development of a new resistant bacterial strain previously thought to be susceptible), as well as when the suspected medicinal product is a vaccine or contraceptive.

For vaccines, cases of lack of therapeutic efficacy should be reported, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccines, waning immunity, or strain replacement. Such a signal may require prompt action and further investigation through post-authorization safety studies as appropriate.

*7.1.7. Expedited reporting of individual case safety reports (ICSRs) and other information related to the safety of medicinal products*

Only valid individual case safety reports should be reported to the competent authorities of Member States. The clock for the reporting of a valid individual case safety report starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the marketing authorization holder, including medical representatives and contractors. This date should be considered as day zero.

Where the marketing authorization holder has set up contractual arrangements with a person or an organization, explicit procedures and detailed agreements should exist between the



marketing authorization holder and the person / organization to ensure that the marketing authorization holder can comply with the reporting obligations. These procedures should in particular specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the competent authorities of Member States.

For individual case safety reports described in the scientific and medical literature, the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where contractual arrangements are made with a person / organization to perform literature searches and / or report valid individual case safety reports, detailed agreements should exist to ensure that the marketing authorization holder can comply with the legal reporting obligations.

When additional significant information is received for a previously reported adverse reaction case, the reporting time clock starts again for the submission of a follow-up report from the date of receipt of the relevant follow-up information. For the purpose of reporting, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case or could change its severity. Non-significant information includes updated comments on the case assessment or corrections of typographical errors in the previous case version.

#### *7.1.7.1. Requirements for expedited reporting of adverse reactions*

Marketing authorization holders should submit to the competent authority of the respective member state within 15 calendar days after initial receipt of the minimum required information by the marketing authorization holder or its authorized representative (Paragraph 7.1.7. of the Guidelines):

- a report of a serious adverse reaction to a medicinal product detected in the territory of the respective member state;
- a report of a serious unexpected adverse reaction to a medicinal product detected in the territories of other countries.

The established reporting time frame should be applied both to primary and follow-up information concerning an adverse reaction to a medicinal product.

Where an adverse reaction case initially reported as serious becomes non-serious, based on new follow-up information, this information should still be reported to the competent authority within 15 calendar days.

#### *7.1.7.2. Adverse reaction reporting method and format*

Individual case safety reports should be submitted by the marketing authorization holder to the competent authority of the member state electronically. The format of individual

case safety reports should conform to the requirements of the International Conference on Harmonisation (ICH) guidelines “Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs)” (E2B).

*7.1.7.3. Requirements for expedited reporting of other drug safety-related information.*

The following important safety information indicating a change in the risk – benefit balance of a medicinal product is subject to expedited reporting within 15 calendar days:

- a higher-than-expected rate of serious adverse reactions, which may have an effect on the risk – benefit balance of a medicinal product;

- limitations to the distribution of the medicinal product, state registration / marketing authorization withdrawal, non-renewal, revocation, or suspension outside the Eurasian Economic Union for safety- and efficacy-related reasons, initiated by either the competent authorities of Member States or the marketing authorization holders for the respective medicinal product;

- an important change in the Summary of Product Characteristics for the medicinal product in other countries due to safety reasons;

- a safety concern detected in the course of a non-interventional post-authorization study, clinical study, or preclinical study;

- safety data obtained as a result of signal-detecting activities, if they can have an effect on the risk – benefit balance of the medicinal product;

- safety concerns associated with off-label use of the medicinal product;

- safety concerns associated with erroneous information included in the Summary of Product Characteristics or labeling of the medicinal product;

- insufficient efficacy (or lack of efficacy) of medicinal products used in life-threatening conditions, as well as vaccines and contraceptive agents;

- safety concerns related to the supply of raw materials.

This safety information should be submitted in writing to the competent authority of the Member State that has authorized the suspected medicinal product. The aforementioned safety- or efficacy-related information for the medicinal product should be submitted immediately, as soon as it becomes known to the marketing authorization holder or its authorized representative. The submitted information should include the aforementioned safety- or efficacy-related data, as well as activities / measures proposed in relation to the suspected medicinal product. The specified aspects of the safety profile should be reflected and analyzed in respective sections of the periodic safety update report for the medicinal product.

## **7.2. Collection of adverse reaction reports**

### ***7.2.1. Responsibilities of the member states***

Each member state should have its own system for collection and registration of suspected adverse reactions detected in its territory and noticed by health care professionals, patients or consumers, or marketing authorization holders.

Each member state should take all appropriate measures to encourage health care professionals working in its territory to submit reports of suspected adverse reactions to the national competent authority. Besides, the competent authority of the respective member state may impose special obligations on health care professionals.

To optimize the adverse reaction reporting procedure, standard structured web-based questionnaires should be easily accessible through competent authorities' drug-related web portals along with information concerning the various ways of submitting information concerning suspected adverse reactions associated with the use of medicinal products.

The competent authorities of Member States of the member states should ensure that all reports of serious adverse reactions detected in their territory and submitted to the respective competent authority and deemed to be valid are included in the common adverse reactions database of the Eurasian Economic Union member states.

Measures should be taken to express acknowledgement for adverse reaction reporting activities, including providing additional information to the reporters.

With regard to reporting adverse reactions by marketing authorization holders, the competent authorities of Member States where the suspected adverse drug reaction took place may engage the marketing authorization holder to follow up these reports.

Each member state should ensure that the competent authority responsible for the monitoring of the circulation of medicinal products in the respective member state is notified of any suspected adverse reaction noticed by employees of any other body, department, establishment, or organization responsible for patient safety in that state and that such reports are entered into the national database. If the report of a suspected adverse reaction was addressed directly to other bodies, departments, organizations, and / or establishments of the respective member state, the respective competent authority responsible for pharmacovigilance should have a data exchange agreement so that such reports can be directed to the competent authority. This requirement also applies to cases of adverse reactions associated with medical errors.

### ***7.2.2. Responsibilities of marketing authorization holders***

Each marketing authorization holder should set up and maintain the system of collection and registration of all reports of suspected adverse reactions that were brought to its

attention, both those provided as spontaneous reports by health care professionals, patients, or consumers, and those obtained during post-authorization studies. Marketing authorization holders should have mechanisms in place to ensure follow-up and further processing of adverse reaction reports.

The responsibility of marketing authorization holders to collect information concerning suspected adverse reactions also applies to reports on medicinal products possession of which cannot be ruled out based on the active substance name, composition, lot number, method of administration, country of the source, or country where the suspected adverse reaction developed.

#### *7.2.2.1. Spontaneous reports*

Marketing authorization holders should register all spontaneous reports on suspected adverse reactions developing in or outside the Eurasian Economic Union. This includes reports of suspected adverse reactions obtained by electronic means or by any other appropriate means. Marketing authorization holders may use their websites to promote the collection of information on suspected adverse reactions by providing adverse reaction reporting forms or appropriate contact details for direct communication.

#### *7.2.2.2. Solicited reports*

Marketing authorization holders should register all reports on suspected adverse reactions developing in or outside the Eurasian Economic Union and detected during post-authorization studies. Such solicited reports include reports obtained with organization data collection systems initiated, managed, or financed by marketing authorization holders. They also include non-interventional post-authorization studies, compassionate drug use programs, named patient drug use programs for unauthorized medicinal products, other patient support and disease monitoring programs, registries, patient support programs, and collection of efficacy or patient compliance information.

Marketing authorization holders should have mechanisms in place to enable them to collect complete and comprehensive information from initial spontaneous reporting with the aim to ensure appropriate assessment and implementation where the requirements for expedited reporting to the competent authorities of Member States are applicable.

##### *7.2.2.2.1. Reports from non-interventional studies*

With regard to data obtained in the course of non-interventional studies, a distinction should be made between studies with direct collection of primary data from patients and health care professionals and study designs based on secondary data use, such as studies that involve review of medical records or electronic records in the health care system, systematic revisions, or meta-analysis.

A report should be prepared when the reporter or marketing authorization holder presumes that there is at least a possible causal relationship with the suspected medicinal product. Adverse event reports where the causal relationship is considered to be uncertain should be included in the final study report.

With regard to non-interventional studies with direct collection of primary data from patients and health care professionals, reports should be submitted on adverse reactions where the reporter or marketing authorization holder presumes that there is at least a possible causal relationship with the suspected medicinal product. The investigator should report to the competent authorities of Member States (if applicable) on other adverse reactions suspected to be associated with the use of medicinal products that are not studied and where there is no interaction with the investigational medicinal products.

With regard to non-interventional studies based on secondary data use, no reporting of detected adverse reactions is required. All data concerning detected adverse reactions should be summarized in the final study report.

In case of any doubts, the marketing authorization holder may consult the respective competent authorities of Member States of the member state concerning the requirements for adverse reaction reporting.

The marketing authorization holder should follow the national legislation of member state on suspected adverse drug reactions submission requirements to independent Ethics Committees and investigators.

#### *7.2.2.2.2. Compassionate drug use programs, named patient drug use programs for unauthorized medicinal products*

If the marketing authorization holder or health care professional has been notified or has detected a suspected adverse reaction within a compassionate drug use program or a named patient drug use program for an unauthorized medicinal product, adverse reactions should be reported in the following manner:

- If an adverse reaction was detected as part of an active search, only adverse reactions deemed by the source or marketing authorization holder to have at least a possible causal relationship with the use of the suspected medicinal product should be reported. These reports should be considered as solicited adverse reaction reports.

- If an adverse drug reaction was detected not as part of an active search or by request, all undesirable and unintentional adverse reactions to the medicinal product should be considered as unsolicited suspected adverse reaction reports; they should be reported in the appropriate manner.

#### *7.2.2.2.3. Patient support program*

A patient support program is an organized system where a marketing authorization holder receives and collects information relating to the use of a medicinal product by big patient groups. Examples include post-authorization patient support and disease management programs, surveys of patients, information gathering on patient compliance, and monitoring of compensation/re-imburement schemes.

An active search for adverse drug reactions may be undertaken within various organized data collection systems; in this case, they should be deemed as solicited reports. Only adverse drug reactions deemed by the reporter or marketing authorization holder to have at least a possible causal relationship with the use of the suspected medicinal product should be reported.

If an adverse drug reaction was detected within an organized data collection system not as part of an active search or by request, all undesirable and unintentional adverse reactions to the medicinal product that have been reported to the marketing authorization holder by a health care professional or a patient should be considered as unsolicited suspected adverse reaction reports; they should be reported in the appropriate manner.

#### 7.2.2.3. *Reports published in scientific and medical literature*

Marketing authorization holders should monitor publications in the scientific and medical literature in all countries that have authorized respective medicinal products, and submit reports on found adverse reactions to the competent authorities of Member States according to legal requirements of the member states, International Treaties and legislation of the Union.

The following adverse reaction reports (information) detected during monitoring of scientific medical literature are not to be expeditedly reported:

- when ownership of the medicinal product by the marketing authorization holder can be excluded on the basis of the active substance name, composition, method of administration, country of the source, or country where the suspected adverse reaction developed.
- reports based on information from scientific publications that provide summary analysis of data obtained from publicly available databases or those presenting patient information in tabulated or line listing format. This type of articles describes adverse drug reactions, which occur in a group of patients administered a certain medicinal product with the aim of identifying or quantifying a safety hazard related to a medicinal product. Such articles are often related to pharmacoepidemiological studies and their main objective is to detect / evaluate specific risks that could affect the overall risk – benefit balance of a medicinal product.

Safety information presented in such scientific articles should be reviewed in respective sections of the periodic safety update report and be taken into account when considering the

impact on the risk – benefit balance of a medicinal product. Any new safety information that might affect the risk – benefit balance of a medicinal product should be notified immediately to the competent authorities of Member States of the member state that has authorized the medicinal product.

*7.2.2.4. Suspected adverse reactions related to quality defect or falsified medicinal products*

When a report of suspected adverse reactions is associated with a suspected or confirmed falsified medicinal product or quality defect of a medicinal product, a valid individual case safety report should be reported.

In these cases, in order to protect public health, it may become necessary to implement urgent measures, such as the recall of one or more defective batch(es) of a medicinal product from the market. Marketing authorization holders should have a system in place to ensure that reports of suspected adverse reactions related to falsified medicinal products or to quality defects of a medicinal products are assessed and investigated in a timely fashion. In case of confirmed quality defect marketing authorization holder should immediately notify the manufacturer of the medicinal product and the competent authorities of Member States of member states.

*7.2.2.5. Suspected transmission via a medicinal product of an infectious agent*

Any microorganism, virus, or infectious particle (for instance, prion, protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

A suspicion of transmission of an infectious agents via a medicinal product should be regarded as a serious adverse reaction and should be expeditedly reported in accordance with the requirements of the member states legislation. This requirement also applies to vaccines.

A transmission of an infectious agent via a medicinal product may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product. Special attention should be on the detection of infections / infectious agents known to be potentially transmitted via a medicinal product, but the occurrence of unknown agents should also always be considered.

In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (for instance, injection / administration) and the source (for instance, contamination) of the infection and the clinical conditions of the patient at the time of the presumed infection (immuno-suppressed condition / previous vaccination).

Confirmation of contamination (including inadequate inactivation / decreased virulence

(attenuation) of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect.

*7.2.2.6. Period between the submission of the marketing authorization application and the granting of the marketing authorization*

In the period between the submission of the marketing authorization application and the granting of the marketing authorization, information that could impact on the risk - benefit balance of the medicinal product under evaluation may become available to the marketing authorization holder. It is the responsibility of the marketing authorization holder to ensure that this information is immediately submitted to the competent authority of the Member State where the application is under assessment.

*7.2.2.7. Period after suspension, revocation or withdrawal of marketing authorization*

The marketing authorization holder shall continue to collect any reports of suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorization. Reporting should still be continued for cases meeting the expedited reporting requirements.

Where a marketing authorization is withdrawn or revoked, the competent authorities of Member States should encourage former marketing authorization holder to continue collecting reports of suspected adverse reactions to, for instance, facilitate the review of delayed onset adverse reactions or of retrospectively notified adverse drug reactions.

*7.2.2.8. Period during a public health emergency*

A public health emergency is a public health threat duly recognized by the World Health Organization (WHO). In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified on the official websites of the member states' competent authorities.

*7.2.2.9. Reports from class action lawsuits*

Stimulated reports arising from class action lawsuits should be managed as spontaneous reports. Reports should be submitted only for adverse reactions where the reporter or marketing authorization holder presumes that there is at least a possible causal relationship with the suspected medicinal product. In these cases, expedited reporting should be done in accordance with the legally established criteria of Eurasian Economic Union and member states.



### **7.3. Preparation of individual case safety reports**

*7.3.1. Information on suspected, interacting, and concomitantly administered medicinal products.*

An adverse reaction report should specify any suspected, interacting, and / or concomitantly administered medicinal products along with the dosing regimens and the treatment start and end dates. With regard to combination medicinal products containing more than one active substance, each active substance should be specified separately.

Where a case of adverse reactions is reported to be related only to a therapeutic class, it is considered incomplete and does not qualify for expedited adverse reaction reporting. Efforts should be made to follow-up the adverse reaction in order to collect the missing information regarding the suspected medicinal product.

*7.3.2. Suspected adverse reaction*

The report of suspected adverse reaction should contain the type or indicated or description of suspected adverse reaction report.

*7.3.3. Case narrative and causality assessment*

For each individual case safety report, all available information on the respective adverse reaction should be presented. The information shall be presented in a logical time sequence, in the chronology of the patient's experience, including clinical course, therapeutic measures, outcome and follow-up information obtained. The narrative should serve as a comprehensive, stand-alone "medical report" containing all known relevant clinical and related (laboratory, diagnostic, and other) information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions and their outcomes, relevant laboratory evidence, and any other information that supports or refutes the suspected adverse reactions. If applicable, any important relevant autopsy or post-mortem findings should also be summarized.

The competent authorities of Member States and marketing authorization holders may comment on the causal relationship between the suspected medicinal product and the adverse reaction, in addition to the causality assessment of the source (reporter), if such is available.

*7.3.4. Results of tests and instrumental investigations*

The adverse reaction description should capture the results of tests and procedures performed to diagnose or confirm the reaction / event, including those tests done to investigate a non-drug cause, (for instance, serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative test results should be reported.

*7.3.5. Follow-up information*

The sender of an adverse reaction report should immediately submit follow-up

information on the adverse reaction if any new important medical information is obtained. Important new information includes, for instance, new suspected adverse reactions, a change in the causality assessment, and any new information or data on changes in initial (previous) information, if this information has an impact on adverse reaction's medical assessment. Identification of important new information requiring expedited reporting always necessitates medical judgement.

Situations where the seriousness criteria and / or causality assessment are downgraded for certain cases (for instance, follow-up information leads to a change of the seriousness criteria from serious to non-serious; causality assessment is changed from any level to unlikely related) should also be considered as significant changes and reported in accordance with the expedited information submission requirements.

When follow-up information only insignificantly alters the initial data and adverse reaction assessment, it should not be expeditedly reported. Examples of minor changes include insignificant changes in some dates, with no effect on the interpretation or submission of the case, or correction of misprints in the previous version of the case. Nevertheless, medical expert opinion should be obtained with regard to the relevance of the follow-up information, because formal assessment may be insufficient in some cases (for instance, a date of birth change may be a significant change in the patient's age information).

#### *7.3.6. Case withdrawal*

A withdrawn case is a case that should no longer be taken into account in the assessment procedures. A case should be withdrawn if it is found out that the entire case was a mistake or in the event of duplicate reports. The case withdrawal procedure includes notification of the recipient by the sender that the case is no longer valid. The report, however, should be retained in the sender's pharmacovigilance database.

### **7.4. Collaboration with the World Health Organization**

The competent authorities of Member States of the member states should ensure regular submission to the World Health Organization Collaborating Centre of reports concerning suspected adverse reactions to medicinal products detected in their territory, so that they are included in the adverse reactions database of the World Health Organization.

## **8. PERIODIC SAFETY UPDATE REPORT**

A periodic safety update report (PSUR) is a pharmacovigilance document intended to provide an evaluation of the benefit-risk balance of a medicinal product for submission by the marketing authorization holder at defined time points during the post-authorization phase.

The competent authorities of the Eurasian Economic Union member states should evaluate PSURs to determine possible new detected risks and their impact on the assessment of the benefit-risk balance of the medicinal product. Based on the results of the evaluation, the competent authority shall determine if there is a need for further safety or efficacy studies / trials for the medicinal product, certain regulatory actions with regard to the regulatory status of the medicinal product, or introducing variations to the Summary of Product Characteristics for the medicinal product with the aim to ensure a favourable benefit–risk balance.

### **8.1. Objectives of the periodic update safety report (PSUR)**

8.1.1. The main objective of a PSUR is to present a comprehensive and critical analysis of the –benefit-risk balance of the medicinal product taking into account all new safety-related information and its cumulative impact on the safety and efficacy profile of the medicinal product. The PSUR is therefore a tool for post-authorization evaluation of the –benefit-risk balance of a medicinal product at defined time points in the lifecycle of the product.

8.1.2. The marketing authorization holder should constantly evaluate and analyse the impact of new data on the benefit-risk balance, re-evaluate this parameter, and determine the need to optimize the –benefit-risk balance by introducing effective risk management and risk minimization measures when new safety information on a medicinal product is detected in the post-authorization phase.

### **8.2. Principles for the evaluation of the –benefit-risk balance within PSURs**

Benefit-risk evaluation should be carried out constantly throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimization activities. This evaluation and analysis should be based on safety and efficacy information collected throughout the corresponding time intervals (reporting periods).

*The evaluation should include the following stages:*

8.2.1 Critically examining the safety information which has emerged during the reporting period to determine whether it has generated new possible detected signals, led to the

identification of new potential or identified risks, or contributed to knowledge of previously identified risks.

8.2.2 Critically summarizing all relevant new safety and efficacy information of the reporting period (obtained either within clinical studies / trials or in everyday medical practice) and evaluation of the impact of this information on the –benefit-risk balance of the medicinal product.

8.2.3 Conducting an integrated benefit-risk analysis based on the cumulative information available since the date of the first marketing authorisation of the medicinal product or the date of the first authorization for the conduct of an interventional clinical trial in any country.

8.2.4 Summarizing any risk minimization actions that may have been taken or implemented , as well as those that are planned to be implemented.

8.2.5 Outlining plans for signal or risk evaluations and / or proposals for additional pharmacovigilance activities.

### **8.3 Principles for the preparation of PSURs**

The marketing authorization holder shall prepare a single PSUR for all manufactured medicinal products containing the same active substance or the same combination of active substances with information covering all the authorized indications, routes of administration, pharmaceutical forms and dosing regimens. Where relevant, data relating to a particular indication, pharmaceutical form, route of administration, or dosing regimen, shall be presented in a separate section of the PSUR and any description and safety profile analysis shall be addressed accordingly, while no separate PSUR is necessary. There might be exceptional scenarios where the preparation of separate PSURs might be appropriate (for instance, in the event of different formulations for entirely different indications for a medicinal product, comparing to its other pharmaceutical forms).

### **8.4. Contents of the PSUR**

8.4.1. The PSUR shall be based on all available data which has emerged since the the first marketing authorization date and shall focus on new information obtained in the reporting period. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit - risk assessment.

The PSUR shall provide summarizing information for all sources of important efficacy and safety data, which should be taken into account when performing the scheduled benefit – risk assessment and possessed by the marketing authorization holder. This information

includes:

summarizing information concerning the medical use:

- spontaneous reporting data;
- medical literature data;
- data obtained with active monitoring techniques (such as analysis of internal or external databases);
- ongoing safety signals being reviewed and assessed by the marketing authorization holder;
- information obtained from marketing or distribution partners;

summarizing information from clinical studies / trials:

- summarizing data from ongoing clinical studies / trials or other clinical studies / trials being conducted by the marketing authorization holder or its representative or clinical studies / trials completed during the reporting period;
- data on therapeutic use of the investigational medicinal product;
- observational or epidemiological studies data;
- data on product usage and drug utilisation studies for the medicinal product;
- preclinical studies data (toxicological studies and studies conducted in vitro);
- data from clinical studies being conducted by partners of the marketing authorization holder in the development or marketing of the medicinal product;
- data from clinical studies demonstrating a lack of therapeutic efficacy, which may have an impact on the benefit - risk assessment for the medicinal product;

summarizing information from other sources:

- data from other sources related to the efficacy or safety evaluation of medicinal products of a similar pharmacotherapeutic class;
- data from other PSUR or development safety update reports (such as contracted partners or study initiators);
- important information obtained after the PSUR has been prepared.

**8.4.2.** *A PSUR should include the following sections:*

*8.4.2.1. Title page, including signature of the person responsible for the PSUR preparation*

*8.4.2.2. Executive summary*

*8.4.2.3. Table of Contents of the report:*

*8.4.2.4. Introduction*

8.4.2.5. *Worldwide marketing authorization status*

8.4.2.6. *Actions taken in the reporting period due to obtained safety data related to the medicinal product*

8.4.2.7. *Changes to reference safety information for the medicinal product*

8.4.2.8. *Estimated patients exposure*

- a) Cumulative subject exposure in clinical trials
- b) Cumulative patient exposure from marketing experience

8.4.2.9. *Data in summary tabulations*

- a) Reference information
- b) Cumulative summary tabulations of serious adverse reactions from clinical trials
- c) Cumulative summary tabulations from post-authorization data sources

8.4.2.10. *Summaries of significant findings from clinical trials during the reporting period;*

- a) Completed clinical trials
- b) Ongoing clinical trials
- c) Long-term follow-up
- d) Other therapeutic use of the medicinal product
- e) New safety data related to fixed dose combination therapies

8.4.2.11. *Findings from non-interventional studies*

8.4.2.12. *Information from other clinical trials and from other sources*

8.4.2.13. *Preclinical studies data*

8.4.2.14. *Literature data*

8.4.2.15. *Other periodic safety update reports*

8.4.2.16. *Lack of therapeutic efficacy of the medicinal product determined in controlled clinical trials*

8.4.2.17. *Important information obtained after PSUR preparation*

8.4.2.18. *Overview of signals (new, ongoing, and closed)*

8.4.2.19. *Signals and risk evaluation*

- a) Summaries of safety concerns
- b) Signal evaluation
- c) Evaluation of risks and new information
- d) Characterization of risk
- e) Effectiveness of risk minimization activities (if applicable)

8.4.2.20. *Benefit evaluation*

- a) Important basic efficacy information on the medicinal product obtained in the

course of clinical studies and in everyday medical practice

b) Newly identified information on efficacy obtained in the course of clinical studies and in everyday medical practice

c) Characterization of benefits

*8.4.2.21. Integrated benefit - risk analysis for authorized indications*

a) Integrated analysis in the context of benefit - risk balance (including medical need and important alternatives)

b) Evaluation of the benefit - risk analysis procedure

*8.4.2.21. Conclusions and proposed following actions in the context of the performed evaluation*

*8.4.2.22. Appendices to the PSUR*

**8.4.3. Title page**

The title page should include the number of the report (reports should be numbered consecutively), the name of the medicinal product, the international birth date, the reporting period (or mention of the extraordinary nature of the submission at the request of the competent authority of a member-state), the date of the report, the marketing authorization holder details, and a statement of confidentiality of the information included in the PSUR. The title page shall be also certified by signature.

**8.4.4. PSUR executive summary**

The purpose of the executive summary is to provide a concise summary of the content and the most important information in the periodic safety update report. This section should contain the following information:

introduction, report number, and reporting period;

medicinal product, its pharmacotherapeutic class, mechanism of action, indication(s), pharmaceutical formulation(s), dose(s), and method(s) of administration;

estimated cumulative clinical trials exposure;

estimated interval and cumulative exposure from this post-authorisation period;

the list of countries in which the medicinal product is authorized;

summary of the overall benefit - risk analysis evaluation;

actions taken and proposed for safety reasons (for instance, significant changes to the Investigator's Brochure at the clinical research stage and to the Summary of Product Characteristics at the post-authorization stage, or other risk minimization activities);

conclusion.

**8.4.5. The executive summary should be followed by the table of contents of the periodic safety update report.**

## **8.5. Requirements for the contents of each PSUR section**

### **8.5.1. PSUR section “Introduction”**

The Introduction should contain the following information:

- the international birth date, the reporting period, and the report sequence number;
- the name of the medicinal product, its pharmacotherapeutic class, mechanism of action, indication(s), pharmaceutical formulation(s), dose(s), and method(s) of administration;
- a brief description of the population(s) being treated with the medicinal product or enrolled in the clinical studies;
- a brief description and explanation of any relevant PSUR information that was not included in the PSUR being submitted.

### **8.5.2 PSUR section “Worldwide marketing authorization status”**

This section of the PSUR should contain a brief narrative overview including: the date of the first authorizations worldwide, the authorized indications, the authorized pharmaceutical forms and dosages, also specifying the marketing authorizations valid at the time of preparation of the PSUR.

### **8.5.3. PSUR section “Actions taken in the reporting period due to obtained safety data related to the medicinal product”**

This section of the PSUR should include a description of significant actions related to safety that have been taken worldwide during the reporting period, related to either investigational uses in clinical trials or marketing experience by the competent authorities of a member-state, the marketing authorization holder, sponsor of clinical trials, data monitoring committee, ethics committee, and that had either:

- a significant influence on the benefit-risk balance of the authorized medicinal product;
- an impact on the conduct of a specific clinical trial or on the overall clinical development programme of the medicinal product.

The reason for each action should be provided and any additional relevant information should be included in this section (as appropriate).

*8.5.3.1. Examples of actions taken in regard to the investigational medicinal product may include:*

- a) refusal to authorize a clinical study / trial for safety or ethical reasons;
- b) partial or complete clinical study / trial suspension or early termination of an ongoing clinical study / trial because of safety findings or lack of therapeutic efficacy;
- c) withdrawal of the investigational medicinal product or comparator;
- d) failure to obtain marketing authorization for an indication studied in a clinical trial, including voluntary withdrawal of a marketing authorization application;



- e) implementation of risk management activities, including:
- study / trial protocol modifications due to safety or efficacy concerns (such as dose regimen changes, changes in study inclusion / non-clusion criteria, intensification of subject monitoring, limitation in study / trial duration);
  - restrictions in the study population or indications;
  - changes to the informed consent document relating to safety concerns;
  - medicinal product formulation changes;
  - addition by competent authorities of member-states of a special safety-related reporting requirement;
  - special issuance of a communication to investigators or health care professionals;
  - plans for new studies to address safety concerns.

*8.5.3.2. Actions related to an authorized medicinal product include:*

- a) failure to obtain a marketing authorization renewal;
- b) suspension or withdrawal of a marketing authorization;
- c) introduction of risk minimization plan, including:
  - significant restrictions on distribution or introduction of other risk minimization measures;
  - significant changes in the Summary of Product Characteristics that might affect the development programme, including restrictions on use or population treated with the medicinal product in question;
  - special communications to health care professionals;
  - post-marketing study requirements imposed by the competent authorities of member-states.

***8.5.4 PSUR section “Changes to reference safety information for the medicinal product”***

This PSUR section should list any significant changes made to the reference safety information within the reporting period. Such significant changes might include information relating to contraindications, warnings, precautions, additional information on serious adverse drug reactions, adverse drug reactions of special interest, drug interactions, important findings from ongoing or completed clinical studies / trials, and significant non-clinical findings (for instance, carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR. The PSUR Appendix should contain the new version of the reference safety information for the medicinal product containing respective changes.

The marketing authorization holder should also provide information concerning

changes to the Summary of Product Characteristics that either have been made or are being made on the basis of the renewed Core Safety Information of the marketing authorization holder, which should be included in the Appendix.

#### **8.5.5. PSUR section “Estimated patients exposure”**

PSURs shall provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use in medical practice, which shall indicate, where appropriate, how actual use differs from the authorized indicated use based on all data available to the marketing authorization holder, including the results of observational studies on drug utilization.

This PSUR section should provide estimates of the size and nature of the population exposed to the medicinal product (including a brief description of the method used to estimate exposure and the limitations of that method).

Consistent methods for calculating subject / patient exposure should be used across PSURs for the same medicinal product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR, introducing the reason for change.

##### **8.5.5.1. PSUR sub-section “Cumulative subject exposure in clinical trials”**

This section of the PSUR should contain the following information on the patients included in clinical studies / trials (a tabular format is recommended):

a) cumulative number of subjects from ongoing and completed clinical studies / trials exposed to the investigational medicinal product, placebo, and / or active comparator since the development international birth date. It is recognized that for “old products” that have been in the circulation for a long time, detailed data might not be available;

b) more detailed cumulative subject exposure in clinical study / trials should be presented (if available) (for instance, sub-grouped by age, sex, and racial group for the entire development programme);

c) important differences among studies / trials in doses, routes of administration, or patient populations;

d) if clinical studies / trials have been performed in special populations (for instance, pregnant women; patients with renal, hepatic, or cardiovascular system impairment; or patients with clinically relevant genetic polymorphisms), exposure data should be provided as appropriate;

e) when there are substantial differences in time of exposure between subjects randomized to the investigational medicinal product or comparator, or disparities in length of exposure between clinical studies / trials, it can be useful to express exposure in subject-time

(subject-days, -months, or -years);

f) data on investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile assessment, depending on the type of adverse reaction, particularly when patients are exposed to a single dose. Such data can be presented separately with an explanation (as appropriate);

g) if the serious adverse reactions from clinical studies / trials are presented in the summarized information on adverse reactions, the corresponding patient exposure evaluation should also be presented, as far as possible;

h) for individual studies / trials of particular importance, demographic characteristics of subjects should be provided separately.

#### 8.5.5.2. PSUR sub-section “Cumulative patient exposure from marketing experience”

Separate estimates should be provided for cumulative exposure (since the international birth date), when possible, and interval exposure (since the data lock point of the previous PSUR). In this sub-section the estimate of the number of patients exposed should be provided, along with the method used to determine the estimate. Justification should be provided if it is not possible to estimate the number of patients exposed. If it is not possible to estimate the number of patients exposed alternative estimates of exposure should be presented along with the method used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose (DDD) may also be used to arrive at patient exposure estimates.

The exposure data should be presented according to the following drug use categories:

##### 8.5.5.2.1. Post-authorization (non-clinical study / trial) exposure (use):

An overall estimation of patient exposure should be provided. The data should be presented by sex, age, indications, doses, formulations, and regions, where applicable. Depending upon the medicinal product, other variables may be included as relevant (such as number of performed vaccinations, method of administration, and duration of treatment).

When there are patterns of adverse reaction reports indicating a safety signal, exposure data within relevant patient subgroup should be presented, if possible.

##### 8.5.5.2.2. Post-authorization use in special populations:

Where post-authorization use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data may include non-interventional studies designed to obtain this information in special population subgroups, including registries. Populations to be considered

for discussion in this section include, but might not be limited to:

- a) paediatric population;
- b) elderly population;
- c) pregnant or breastfeeding women;
- d) patients with hepatic and / or renal impairment;
- e) patients with other relevant co-morbidity;
- f) patients with disease severity different from that studied in clinical trials;
- g) sub-populations carrying relevant genetic polymorphism(s);
- h) populations with other racial and / or ethnic origins.

#### *8.5.5.2.3. Specific use of the medicinal product*

If the marketing authorization holder becomes aware of a pattern of use of the medicinal product, a brief description of this pattern should be provided and the safety data assessed and interpreted in an appropriate manner. Examples of such patterns of use may include evidence of use for non-authorized indication. If known, the marketing authorization holder may briefly comment on whether other use beyond the recommendations may be linked to clinical guidelines, clinical trial evidence, or an absence of authorized alternative treatments. A quantitative estimate of the volume of such use should be presented, if such data are available.

#### **8.5.6. PSUR section “Data in summary tabulations”**

The objective of this PSUR section is to present adverse reactions and events data obtained in the course of clinical studies by means of summary tabulations. At the discretion of the marketing authorization holder, graphical displays can be used to illustrate specific aspects of the data when useful to enhance perception and understanding.

The rating of a signal to a serious adverse reaction in the summary tabulations should correspond to the classification of this signal resulted from evaluation of individual case safety reports using the seriousness criteria established by the legislation of the member-states and international agreements and acts, which constitute the law of the Union. Seriousness should not be changed specifically for the preparation of data to be included in the PSURs.

##### *8.5.6.1 PSUR sub-section “Reference information”*

This sub-section of the PSUR should specify the version of the coding dictionary used for analysis of adverse events and reactions.

##### *8.5.6.2 PSUR sub-section “Cumulative summary tabulations of serious adverse reactions from clinical trials”*

This PSUR sub-section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the marketing authorization holder’s clinical studies / trials, from the development international birth date to

the data lock point of the current PSUR. The marketing authorization holder should explain any omission of data (for instance, clinical study / trial results might not be available for several years). The tabulation(s) should be organized in accordance with the organ system class classification of adverse reactions for the investigational medicinal product, as well as for the comparator arm(s) (active comparators, placebo). When useful, data must be presented by clinical studies / trials, indications, routes of administration, and other variables.

The following aspects should be considered:

- Causality assessment for rare adverse drug reactions. The summary tabulations should include all serious adverse events both for the investigational medicinal product and for comparators (active comparators and placebo) in order to obtain group comparisons, including comparison of frequencies. It may be useful to present data reflecting the association between the administered dose and the frequency.

- The tabulations should include blinded and unblinded serious adverse events data from clinical studies / trials. Unblinded data might originate from completed clinical trials and individual cases that have been unblinded for certain reasons (such as safety-related reasons or the requirement for expedited reporting). Sponsors of a clinical study / trial and marketing authorization holders should not unblind data for the specific purpose of preparing the PSUR.

- Certain adverse events can be excluded from the clinical trials summary tabulations, but all such exclusions should be explained in the PSUR. For example, adverse events that have been defined in the protocol as “exempt” from expedited reporting and are entered only into the general study database because they are anticipated in the patient population, or those that represent study endpoints.

#### *8.5.6.3. PSUR sub-section “Cumulative summary tabulations from post-authorization data sources”*

This sub-section of the PSUR should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the international birth date of the medicinal product to the data lock point of the current PSUR, and includes adverse reactions derived from non-interventional studies and spontaneous reports, including reports from health care and pharmaceutical professionals, consumers, patients, competent authorities of the member-states, as well as data published in medical literature. Serious and non-serious adverse reactions should be presented in separate tables. The data in the table should be organized in accordance with the organ function class classification. For particularly important safety profile concerns, additional tabulations of adverse reactions can be presented by indication, method of administration, and other parameters.

#### ***8.5.7 PSUR section “Summaries of significant findings from clinical trials during***

***the reporting period”***

The marketing authorization holder should include in the appendix a summary of sponsored interventional clinical studies / trials that have been completed or are ongoing in the reporting period, with the aim to ensure identification, characterization, and quantitative assessment of the risks levels, confirmation of the safety profile of the medicinal product, or assessment of the effectiveness of risk minimization activities.

Whenever possible, data categorized by sex and age (particularly paediatrics versus adults), indication, dosing regimen, and region should be presented.

Signals arising from clinical trial sources should be tabulated in PSUR section “Overview on signals: new, ongoing, and closed”. An assessment of the signals, whether a potential or an identified risk, should be presented. The risk should be evaluated and characterized in PSUR sub-sections “Evaluation of risks and new information” and “Characterization of risk”.

This PSUR section should provide a summary of the clinically important emerging efficacy and safety findings obtained from the following sources within the reporting period:

***8.5.7.1. PSUR sub-section “Completed clinical trials”***

This sub-section of the PSUR should provide a brief summary of clinically important emerging efficacy and safety data obtained from clinical studies / trials completed during the reporting period. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety signals, as well as evidence of new safety signals.

***8.5.7.2. PSUR sub-section “Ongoing clinical trials”***

If the marketing authorization holder is aware of any clinically important information that has arisen from ongoing clinical studies / trials (for instance, through interim safety analyses or as a result of unblinding of subjects with serious adverse events), this sub-section should briefly summarize the newly identified safety concern(s). This section could also include information that supports or refutes previously identified safety signals, as well as evidence of new safety signals.

***8.5.7.3 PSUR sub-section “Long-term follow-up”***

This sub-section should provide information from long-term follow-up that is important from the standpoint of the safety profile, if such long-term follow-up data are available for patients enrolled in clinical studies / trials.

***8.5.7.4. PSUR sub-section “Other therapeutic use of medicinal product”***

This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the marketing authorization holder that follow specific

protocols (for instance, expanded access programmes, compassionate use programmes, particular patient use, and others).

**8.5.7.5. PSUR sub-section “New safety data related to fixed dose combination therapies”**

Unless otherwise specified by the requirements of the competent authorities of member-states, the following data should be presented for combination therapies:

a) If the medicinal product is authorized as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarize important safety findings from the use of the combination therapy.

b) If the product itself is a fixed combination product, this sub-section should summarize important safety information arising from each of the individual components.

**8.5.8. PSUR section “Findings from non-interventional studies”**

This section should summarize relevant safety information or data from non-interventional clinical studies (for instance, observational studies, epidemiological studies, registries, and active surveillance programmes) sponsored by the marketing authorization holder, that became available during the reporting period and impact the assessment of the benefit-risk balance of the medicinal product. This section should include relevant information on various aspects of the safety profile obtained in drug utilization studies.

The marketing authorization holder should include an appendix listing all non-interventional studies sponsored by the marketing authorization holder and conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk minimization measures, which were completed or ongoing during the reporting interval (for instance, post-authorization safety studies).

Progress study reports or final study reports completed during the reporting period should be included in the appendix of the PSUR.

**8.5.9. PSUR section “Information from other clinical trials and from other sources”**

This PSUR sub-section should summarize information relevant to the benefit - risk assessment of the medicinal product from other clinical trial / study sources or from other sources, which were accessible by the marketing authorization holder during the reporting period (for instance, results from meta-analysis of randomized clinical trials, safety information provided by co-development partners, etc).

**8.5.10. PSUR section “Preclinical studies data”**

This PSUR section should summarize significant safety findings from preclinical *in*

*vivo* and *in vitro* studies (for instance, carcinogenicity, reproductive toxicity or immunotoxicity studies) ongoing or completed during the reporting period. An assessment of the impact of obtained data on the safety profile should be presented in Section “Signals and risk evaluation” and Section “Integrated benefit - risk analysis for authorized indications” of the PSUR.

#### **8.5.11. PSUR section “Literature data”**

This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the marketing authorization holder became aware of during the reporting period, when relevant to the medicinal product.

Literature searches for PSURs should be wider than those for individual adverse reaction cases, because they should also include studies with evaluation of safety outcomes in groups of subjects.

The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:

- a) pregnancy outcomes (including termination) with no adverse outcomes;
- b) use in paediatric populations;
- c) compassionate supply, named patient use programmes;
- d) lack of efficacy of a medicinal product;
- e) asymptomatic overdose, off-label use or misuse;
- f) medication error where no adverse events occurred;
- g) important preclinical results.

If relevant and applicable, information on other active substances of the same pharmacological group should be considered in this section.

#### **8.5.12. PSUR section “Other periodic safety updated reports”**

This PSUR section will only apply in certain circumstances where multiple PSURs for a medicinal product are prepared by the marketing authorization holder in agreement with the competent authorities of member-states (for fixed dose combination products or products with multiple indications and / or different formulations). In general, the marketing authorization holder should prepare a single PSUR for a single active substance. In particular cases series of PSURs are prepared for a single medicinal product, according to the decision of regulatory / competent authorities of member-states. In this case the present section of each next PSUR of such series should summarize significant safety findings from other PSURs, if they are not presented elsewhere within the report.

When PSURs for similar medicinal products of other marketing authorization holders, sponsors of clinical studies / trials or other contractual partners are available, based on the



contractual agreements, the marketing authorization holder should summarize significant safety findings obtained from PSURs provided during the reporting period by other parties.

**8.5.13. PSUR section “Lack of therapeutic efficacy of the medicinal product determined in controlled clinical trials”**

If in clinical studies / trials with medicinal products intended to treat or prevent serious or life-threatening illnesses there are data indicating lack of therapeutic efficacy, or lack of therapeutic efficacy relative to established therapy(ies), that could reflect a significant risk to the treated population and thus should be analyzed and summarized in this section of the PSUR.

If applicable to benefit - risk assessment, clinical study / trial data demonstrating lack of therapeutic efficacy of medicinal products not intended for the treatment of life-threatening conditions should be analyzed in this section as well.

**8.5.14. PSUR Section “Important information obtained after PSUR preparation”**

The potentially important safety and efficacy findings that arise after the data lock point but before preparation of the final version of PSUR, should be summarized in this PSUR section. Examples include clinically significant data from new publications, important follow-up data, clinically relevant toxicological findings, and any action that the marketing authorization holder, a data monitoring committee, or competent authorities of member-states have taken for safety reasons related to medicinal products. New individual case safety reports should not be routinely included in the section unless they are considered to constitute an important index case (for instance, the first instance of an important adverse event in human) or an important safety signal.

The data presented in this section should also be taken into account in the sub-section “Evaluation of risks and new information” of the PSUR section “Signals and risk evaluation”.

**8.5.15. PSUR section “Overview of signals (new, ongoing, and closed)”**

The purpose of this section is to provide a comprehensive overview of detected signals (which evaluation has not yet been started), signals received during the period of evaluation of adverse drug reaction, as well as signals with completed evaluation during the reporting period.

The marketing authorization holder should present a brief description of the method used to identify signals, as well as the data sources used to identify signals.

A new signal refers to a signal that has been identified during the reporting period. Ongoing signals are signals being evaluated at the time of the data lock point. Closed signals are signals for which completed during the reporting period. Signals that are both new and closed during the reporting period (as regards their evaluation) should be classified as closed signals.

This section should include tabulated information related to signals ongoing and completed during the reporting period. The table should be included as an appendix to the

report. At the discretion of the marketing authorization holder, this information may also include cumulative data on the signals (including previously closed signals), and specify the date from which the signals were summarized.

A detailed assessment of the signals should be included in PSUR sub-sections “Signal evaluation” and “Evaluation of risks and new information”.

#### **8.5.16. PSUR section “Signals and risk evaluation”**

##### **8.5.16.1. PSUR sub-section “Summaries of safety concerns”**

The purpose of this sub-section is to provide a basic summary of important issues of the safety profile, which are safety concerns for a medicinal product, indicating which new information and new evaluations for each safety issue can be made. The following factors should be considered when determining the importance of each risk aspect:

- a) medical seriousness of the risk related to a medicinal product, including the impact on individual patients;
- b) its frequency, predictability, preventability, and reversibility;
- c) potential impact on public health (frequency of the risk in the population; size of exposed population);
- d) assessment of public acceptability of the risk in case of potential influence of a medicinal product to the public health (for instance, refusal of the vaccination programme).

*8.5.16.1.2. Summarized information should present the available data for the medicinal product since the beginning of the PSUR reporting period, and should reflect the following:*

- important identified risks;
- important potential risks;
- important missing information.

8.5.16.1.3. For medicinal products with an existing safety specification, the information in this sub-section should be the same as the safety specification summary that is current at the start of the reporting period of the PSUR.

For products without an existing safety specification, this sub-section should provide information on the important identified and potential risks and important missing information associated with use of the medicinal product, based on pre- and post-authorization experience. Examples may include the following information:

- a) important adverse reactions;
- b) interactions with other medicinal products;
- c) identified medication errors or mistakes, where no adverse drug reactions developed;

- d) interactions with foods and other substances;
- e) effects of occupational exposure;
- f) pharmacological class effects.

The summary on important missing information should take into account whether there are critical gaps in knowledge for specific safety issues for the target populations.

#### 8.5.16.2. PSUR sub-section “Signal evaluation”

This sub-section of the PSUR should summarize the results of evaluations of safety signals that were closed during the reporting interval. The two main categories to be included in this sub-section are:

a) Those signals that, following evaluation, have been categorized as either a potential or identified risk, including lack of therapeutic efficacy (PSUR section “Lack of therapeutic efficacy of the medicinal product determined in controlled clinical trials”).

b) Those signals that, following evaluation, have been refuted as “false” signals based on scientific evaluation of the currently available information. For this category of signals, a concise description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was deemed as deviating from the signals category. This description may be included in the main text of the PSUR or in an appendix to the report.

8.5.16.2.2. For signals with completed evaluation during the reporting period, it is recommended that the volume and level of detail provided in the description of the signal evaluation should reflect the medical significance of this safety profile aspect for public health, as well as the extent of the available evidence. This information should cover the following aspects:

- a) source or trigger of the signal;
- b) background relevant to the evaluation;
- c) methods of evaluation, including data sources, search criteria, or analytical approaches;
- d) results – (a summary) of critical analysis of the data considered in the signal evaluation;
- e) discussion;
- f) conclusions, including proposed actions.

#### 8.5.16.3. PSUR sub-section “Evaluation of risks and new information”

The marketing authorization holder should provide a critical appraisal of new information relevant to new or previously recognized risks (important or other) that has become available during the reporting period.

This sub-section of the PSUR should include a description and an assessment of all

risks identified during the reporting period, as well as an assessment of the effects of newly available data on previously recognized risks. The sub-section should not include summarizing or duplicate information included in other PSUR sections, but should present an interpretation and assessment of the new information from the standpoint of characterizing the risk profile.

New information should be presented for the following topics:

New potential risks;

New identified risks;

New information on previously identified risks (potential and identified);

Update on important missing information.

A brief description of the important risks should be presented. For risks classified as other or unimportant risks for which new information became available during the reporting interval, it is recommended that the level of detail of the evaluation should be proportional to the available evidence on the respective risk and its medical significance and public health relevance.

Any new information on populations exposed or data generated to address previously missing information should be critically assessed. Unresolved concerns and uncertainties related to the safety profile of the medicinal product should be acknowledged.

#### 8.5.16.4. PSUR sub-section “Characterization of risk”

This sub-section should characterize important identified and important potential risks based on cumulative data (including those not restricted to the reporting interval), and describe important missing information.

8.5.16.4.1. Depending on the nature of the data source, the information on risks should include, where applicable:

- a) frequency;
- b) numbers of cases (numerator) and precision of estimate;
- c) extent of use (denominator) expressed as numbers of patients, patient-months (patient-years), etc., and precision of estimate;
- d) estimate of relative risk and precision of estimate;
- e) estimate of absolute risk and precision of estimate;
- f) impact on the individual patient (effects on symptoms, quality of life);
- g) public health impact;
- h) risk factors (for instance, individual risk factors (age, pregnancy, lactation, hepatic / renal impairment, relevant co-morbidity, disease severity, genetic polymorphism, race and / or ethnicity, dose);
- i) duration of treatment, risk period;

- j) preventability (predictability and the ability to monitor for a “sentinel” symptoms or laboratory marker should be assessed);
- k) reversibility;
- l) potential mechanism; and
- m) strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

8.5.16.4.2. For PSURs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- a) risks relating to the active substance;
- b) risks related to a specific formulation or route of administration (including occupational exposure);
- c) risks relating to a specific population;
- d) risks associated with non-prescription use (for active compounds that are available as both prescription and non-prescription products);
- e) safety concerns related to missing information.

8.5.16.5. *PSUR sub-section: “Effectiveness of risk minimization activities (if applicable)”*

Risk minimization activities include interventions intended to prevent the occurrence of adverse drug reactions associated with the exposure to a medicinal product or to reduce their severity should they occur. The aim of a risk minimization activity is to reduce the probability or severity of adverse drug reactions. Risk minimization activities may consist of routine risk minimization (for instance, a change in the Summary of Product Characteristics) or additional risk minimization activities (for instance, direct health care professional communication / educational materials).

This sub-section shall contain the results of assessments of the effectiveness of risk minimization activities. Relevant information on the effectiveness and / or limitations of specific risk minimization activities for important identified risks that has become available during the reporting period should be summarized. Results of evaluations that became available during the reporting period should be provided in the PSUR appendix.

#### **8.5.17. PSUR section “Benefit evaluation”**

8.5.17.1 PSUR sub-section (“Important basic efficacy information on the medicinal product obtained in the course of clinical studies and in everyday medical practice”)

This sub-section summarizes basic information on the efficacy of the medicinal product

demonstrated in the course of clinical studies and effectiveness demonstrated in everyday medical practice beginning from the start of the reporting period. This information should relate to authorized indication(s) of the medicinal product.

For medicinal products with multiple indications, target populations, and / or routes of administration, the benefit should be characterized separately by these factors.

For medicinal products shown to have significant changes in the safety or efficacy profile in the reporting period, this sub-section should provide sufficient information to support the updated characterization of benefit of the medicinal product reflected in the PSUR sub-section (“Characterization of benefits”). The contents and level of detail provided in this sub-section can vary by medicinal product, including (when applicable) the following aspects:

- epidemiology and disease origin;
- characteristics of benefits (for instance, diagnostic, prophylactic, symptomatic, disease-modifying);
- important endpoints demonstrating benefits (such as effects on mortality, symptoms, and outcomes);
- evidence of efficacy in clinical studies and in medical practice as compared with a comparator drug (for instance, comparative clinical studies with an active comparator, meta-analysis, observational studies);
- trends and / or evidence of benefits presented for essential population subgroups (for instance, those based on age, gender, ethnicity, disease severity, genetic polymorphism), if this is relevant to benefit - risk assessment.

*8.5.17.2 PSUR sub-section “Newly identified information on efficacy obtained in the course of clinical studies and in everyday medical practice”*

For some medicinal products, during the reporting period additional information on efficacy in the course of clinical studies and in medical practice may have become available, that should be presented in this subsection. Separate information on evidence related to unauthorized indications for use should not be included in this sub-section unless relevant for the benefit - risk evaluation.

In this sub-section, particular attention should be given to vaccines, anti-infective agents, or other medicinal products where changes in the therapeutic environment may impact on the benefit-risk balance evaluation over time.

The contents and level of detail of information provided in this sub-section can vary by medicinal product. If no information is obtained during the reporting period, a reference may be made to PSUR section “Important basic efficacy information on the medicinal product obtained

in the course of clinical studies and in everyday medical practice”.

**8.5.17.3 PSUR sub-section “Characterization of benefits”**

This sub-section should provide an integration of the baseline and the new therapeutic benefit information that has become available during the reporting period, for authorized indications.

When there are no new relevant benefit data and no significant changes in the safety profile, this sub-section should provide a reference to the information in sub-section “Important basic efficacy information on the medicinal product obtained in the course of clinical studies and in everyday medical practice”.

When there is new therapeutic benefit information and no significant change in the safety profile in this reporting period, the integration of baseline and new information in this sub-section should be briefly presented.

If significant changes in the safety profile occur or new information is obtained indicating a significantly lower level of therapeutic benefit than that demonstrated at baseline, this sub-section should provide a concise critical evaluation of the evidence on safety and efficacy in the course of clinical studies and in medical practice, mentioning the following information:

- a brief description of the strength of evidence of therapeutic benefit (providing evaluation of comparator(s) efficacy aspects, effect size, statistical rigor, methodological strengths and deficiencies, consistency of findings across trials / studies);
- new information that challenges the validity of a surrogate endpoints (if used); clinical relevance of the therapeutic effect size;
- generalizability of treatment response across the target patient populations (for instance, information that demonstrates lack of treatment effect in any sub-population);
- adequacy of characterization of “dose-therapeutic response”; duration of effect;
- comparative efficacy;
- a determination of the extent to which efficacy findings from clinical trials are generalizable to patient population treated in medical practice.

**8.5.18. PSUR section “Integrated benefit - risk analysis for authorized indications”**

The marketing authorization holder should provide in this section an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. This section should provide a critical analysis and integration of the information of the previous sections as regards

benefit and risks, and should not duplicate the information presented in PSUR sub-sections “Evaluation of risks and new information” and “Characterization of benefits”.

*8.5.18.1. PSUR sub-section “Integrated analysis in the context of benefit – risk balance (including medical need and important alternatives)”*

This sub-section should provide a brief description of the medical need for the medicinal product in the authorized indications and summarized alternatives (medical, surgical or other indications; including no treatment).

*8.5.18.2. PSUR sub-section “Evaluation of the benefit - risk analysis procedure”*

A –benefit-risk balance is specific to an indication and target population. Therefore, for medicinal products authorized for several indications, –the benefit-risk balance should be evaluated by each indication individually. If there are important differences in the –benefit-risk balance among populations within one indication, the benefit - risk evaluation should be presented separately and by population subgroups (if applicable).

*8.5.18.2.1. Major aspects of benefit and risks:*

- The key information related to benefits and risks and considered in the previous sections should be integrated in order to evaluate their balance.

- The context of use of the medicinal product should be considered (the recovery, prevention, diagnostics); the severity and seriousness of the disease; and the population to be treated (relatively healthy; chronic illnesses).

- With respect to the benefits, factors to be considered include its nature, clinical importance, duration of effect, and generalizability, evidence of efficacy in non-responders to alternative treatments, the effect size, and individual elements of benefit.

- With respect to risk, factors to be considered include its clinical importance (for instance, nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and also risk aspects related to use for unauthorized indications, new indications, misuse.

- When formulating the benefit - risk evaluation, the strengths, weaknesses, and uncertainties of the evidence should be considered with description of their impact to the evaluation.

Limitations of the provided assessment should be discussed.

*8.5.18.2.2. A description and reasoning for the methodology used to develop the benefit - risk evaluation should be presented:*

- the assumptions, considerations, weighting that support the conclusions of the benefit - risk evaluation;

- comments concerning the appropriateness of the presented benefit - risk assessment



format and their comparing;

- if a quantitative assessment of benefit - risk is provided, a summary of the methods used for this assessment should be included;

- economic considerations (for instance, “cost - effectiveness”) should not be considered in the benefit - risk evaluation.

**8.5.19. PSUR section “Conclusions and proposed following actions in the context of performed evaluation”**

The concluding PSUR section should include a conclusion on the implications of new information that arose during the reporting period in terms of the overall evaluation of benefit - risk for each authorized indication, as well as for patient subgroups (if appropriate).

Based on the evaluation of the cumulative data on safety and the benefit - risk balance analysis, the marketing authorization holder should assess the need for changes to the product information and propose a context for changes as appropriate.

The conclusions should include preliminary proposals to optimize or further evaluate the risk - benefit balance for further discussion with the relevant competent authorities of the member-states. This may include proposals for risk minimization activities.

For medicinal products with a pharmacovigilance and risk minimization plan, the proposals should be incorporated into the pharmacovigilance plan and the risk minimization plan.

**8.5.20. The PSUR section “Appendices to the PSUR”**

A PSUR should contain the following appendices:

- Reference information;
- Cumulative summary tabulations of serious adverse events from clinical studies / trials;
- Cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing experience;
- Tabular summary of safety signals;
- Assessment of the signals (if applicable);
- Listing of all post-authorization safety studies.

**8.6 Quality systems for PSURs at the level of the Marketing Authorization Holder**

The marketing authorization holder should have in place structures and processes for the preparation, quality control, review, and submission of PSURs including follow-up control

during and after their assessment. These structures and processes should be described by means of procedures, implemented as written documents in the marketing authorization holder's quality system.

There are a number of areas in the pharmacovigilance process that can directly impact the quality of PSURs (for example, case management of spontaneous and clinical study reports, literature screening, signal identification, validation, and assessment, additional pharmacovigilance and post-marketing research activities, procedures for processing and integration of information for benefits and risks evaluation, etc). The quality system should describe the links between the processes, the communication channels, and the responsibilities s regards the procedure of gathering all the relevant information for the production of PSURs. Documented procedures should be elaborated and implemented onquality control checks of the processes to ensure the completeness and accuracy of the data presented in the PSURs. The importance of an integrated approach to benefit - risk evaluation should ensure the necessity of cross departmental or divisions input to PSUR preparation.

The PSUR should also contain the assessment of specific safety issues requested by competent authorities of member-states. The marketing authorization holder should have mechanisms in place to ensure that the requests made by competent authorities of member-states during the time of their PSUR assessment are properly managed and answered.

The provision of the data included in the summary tabulations should undergo source data verification against the marketing authorization holder's safety database to ensure accuracy and completeness of the adverse events and reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.

An appropriate quality system should be used by the marketing authorization holder in order to avoid failure of the marketing authorization holder to comply with legal requirements, such as:

- non-submission: complete non-submission of PSURs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the competent authorities of member-states);
- unjustified omission of information requested;
- poor quality reports (poor documentation or insufficient information or evaluation provided to perform assessment of the new safety information, safety signals, risk evaluation, benefit evaluation and integrated benefit - risk analysis, misuse not highlighted, absence of use of standardized medical terminology, and inappropriate dismissal of cases, no reported risk factors);

- submission of a PSUR where previous requests from competent authorities of member-states have not been addressed.

Any significant deviations from the procedures relating to the preparation or submission of PSURs should be documented and the appropriate corrective and preventive action should be taken. This documentation should be available at all times.

When the preparation of the PSUR is delegated to third parties, the marketing authorization holder should ensure that they are subject to a quality system compliant with the law of the Union and legislation of the member-states.

### **8.7. Training of staff members related to the PSUR process**

It is the responsibility of the qualified person responsible for the pharmacovigilance to ensure that the personnel, including pharmacovigilance, medical information, and quality control personnel involved in the preparation, review, quality control, assessment and submission of PSURs, are adequately qualified, experienced and trained. Specific training should be in place for the different aspects of the process, knowledge, and skills related to pharmacovigilance. Training should cover the aspects of the law of the Union and legislation of the member-states, guidelines, scientific evaluation of data and written procedures related to the PSUR preparation. Training records should demonstrate that it was delivered prior to performing respective PSUR-related activities.

### **8.8. The PSUR submission procedure**

#### **8.8.1. *Standard submission schedule of PSURs***

The periodicity and timeline for submission of PSURs for medicinal products are determined in accordance with the list to be approved by the competent authorities of the member states.

For medicinal products with an international nonproprietary name or group name not included in the aforementioned list, the periodicity for submission of PSURs is as follows:

- every 6 months from the international birth date for the first 2 years;
- annually for the next 2 years;
- every 3 years thereafter.

The time from the data lock point to the submission of a PSUR should not exceed 90 calendar days.

#### **8.8.2. *Extraordinary PSUR submission***

A PSUR should be submitted immediately. The preparation of PSUR should be performed within 60 calendar days from the date a written request is received from the

competent authority of a member state.

### **8.8.3. *PSUR submission format***

A PSUR should be submitted in electronic format enabling text search in Russian or English, with mandatory translation into Russian of the following sections: the Executive summary, Integrated benefit - risk analysis for authorized indications, and Conclusion. At the request of the competent authority of a member-state, the marketing authorization holder must submit a Russian translation of any other PSUR sections within 30 calendar days after the receipt of such request.

### **8.9. PSUR assessment procedure in the territory of member states**

The competent authorities of member states must ensure assessment of PSURs with the aim to determine their compliance with requirements of the law of the Union and legislation of member states, as well as to evaluate possible changes in the safety profile of the medicinal product and the impact of these changes on the benefit-risk balance of the medicinal product in question.

## 9. SIGNAL MANAGEMENT

### 9.1. Structures and processes

#### 9.1.1. Sources of signals and their processing

**9.1.1.1.** The sources of signals include all data obtained when using medicinal products including non-clinical, clinical, pharmacovigilance data and quality control system data. Data may include findings from spontaneous reporting systems, active surveillance systems, non-interventional studies, clinical studies, and other sources of information.

**9.1.1.2.** Signals from spontaneous reports may be detected in ICSRs, included in adverse reaction databases, articles from the scientific literature, PSURs or other information provided by MAHs in the context of regulatory procedures (e.g. variations and updates, renewals, post-authorization commitments) or from continuous monitoring of the risk-benefit balance of medicinal products.

**9.1.1.3.** Signals may arise from a wide range of different study/trial types, including non-clinical, interventional and non-interventional studies, systematic reviews and meta-analyses. Different types of active monitoring may assist in the identification of signals and stimulate the process of reporting of certain types of adverse reactions by specialists.

**9.1.1.4.** The other sources of information include the Internet, digital media (such as publicly available web-sites, social networks, blogs) or other systems via which the patients and consumers may report information about experience of the development of adverse reactions to medicinal products.

#### 9.1.2. Methodology for signal processing

**9.1.2.1.** Signal detection should follow a structured and recognized methodology, which may vary depending on the type of medicinal product concerned.

**9.1.2.2.** In order to assess the evidence basis of a signal, a structured and recognized methodology should be applied taking into account the clinical significance, causal relationship, consistency of the data, consistency of exposure-reaction degree, causal relationship, biological plausibility, experimental findings, data on possible analogous by the nature of an event.

**9.1.2.3.** Different factors may be taken into account for the prioritization of signals, namely: whether the revealed association or a medicinal drug is new, factors relevant to the strength of the association, the seriousness of the reaction involved and factors of the documentation of a report.

#### 9.1.3. The signal management process

##### 9.1.3.1. Introduction

**9.1.3.1.1.** The signal management process covers all steps from detecting signals to

development of recommendations. The rules of signal management relate to all parties concerned participating in safety control of the authorized medicinal products.

9.1.3.1.2. The signal management process includes the following steps:

- a) Signal detection;
- b) Signal validation;
- c) Signal analysis and prioritization;
- d) Signal assessment;
- e) Recommendations for action;
- f) Exchange of information.

9.1.3.1.3. Although these steps generally follow a logical sequence, the wide range of sources of information available for signal detection may require some flexibility in the conduct of signal management e.g.:

- when signal detection is primarily based on a review of ICSRs, this procedure may include verification and preliminary prioritization of a detected signal;
- when a signal is detected from cumulative results of a study, it is usually not possible to assess each ICSR, and validation may require collection of additional data.

Recommendations for action (followed by decision in accordance with the applicable legislation) and exchange of information are components to be considered at every step of the process.

#### *9.1.3.2. Signal detection*

9.1.3.2.1. Whichever methods are employed for the detection of signals, the following principles should be exercised:

- a) The method used should be appropriate for the data set; for example, the use of complex statistical tools may not be appropriate for smaller data sets;
- b) Data from all appropriate sources should be considered;
- c) Systems should be in place to ensure the quality of the signal detection activity;
- d) Any results of a review of cumulative data should be assessed appropriately by a qualified person in a timely manner;
- e) When a public health threat is detected, immediate and effective actions should be taken;
- f) The process of signal detection should be adequately documented including the rationale for the method and periodicity of the signal detection activities.

9.1.3.2.2. Detection of safety signals may be performed based on a review of ICSR databases, statistical analysis in large databases, or from a combination of both.

##### *9.1.3.2.2.1. Review of ICSRs*

ICSRs may originate from a spontaneous reporting system, active form of monitoring, clinical studies or medical literature. Even a single report of a serious or severe adverse reaction (for example, one case of anaphylactic collapse) may be sufficient to raise a signal and to take further actions. The information due to assessment should include the number of reports (after exclusion of duplicates and non-valid reports), the patient's demographics (e.g. age and gender), the suspected medicinal drug (e.g. dose administered) and the adverse reaction (e.g. signs and symptoms), the temporal association, the clinical outcome in relation to drug continuation or discontinuation, the presence of potential alternative causes of adverse event, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship.

#### 9.1.3.2.2.2. Statistical analyses of large databases

Various statistical methods have been developed to automatically identify signals depending on disproportionate reporting, i.e. higher reporting for a suspected adverse reaction for a relevant active substance/medicinal product compared to other active substances/medicinal products in the database. Use of statistical methods may not be feasible in all situations. The data set, the completeness of the available information and the severity of the adverse reaction should be taken into account when considering the use of statistical methods and the selection of criteria for signal detection.

The periodicity of statistical analysis of database and statistical report may vary according to the characteristics of active substance/medicinal product, its indication and potential or identified risks.

#### 9.1.3.2.2.3. Combination of statistical methods and review of ICSRs

Statistical reports may be designed to identify suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical association. Such filtering methods may facilitate the selection of the most important ICSRs to be reviewed at first stage. The thresholds used in this filtering process (for example, at least 3 cases reported) may vary according to the clinical importance of a suspected adverse reaction and a signal, the public health impact and the extent of usage of medicinal products.

Where automatic screening is used in the process of signal detection, the corresponding ICSRs should be individually reviewed.

Irrespective the statistical method used the signal detection should always involve clinical evaluation. A statistical method is a supporting tool in the process of signal detection and validation.

#### 9.1.3.3. Signal validation

9.1.3.3.1. Upon signal detection, further data evaluation is implemented to verify and confirm that the available information contains sufficient evidence demonstrating the existence of a new potentially causal relation or a new aspect of a known relation. The results of validation determines the necessity of further assessment of a signal.

To validate a signal irrespective of its source the following should be taken into account:

9.1.3.3.1.1. Clinical relevance including, for example:

- strength of evidence for the cause of an event (e.g. number of reports with regard to exposure, temporal association, plausibility/probability of adverse reactions, results of withdrawal and repeated administration of a medicinal product, alternative explanation/other casual factors);
- seriousness of an adverse reaction and its outcome;
- novelty of the reaction (e.g. new and serious adverse reactions);
- clinical context (e.g. clinical syndrome including other reactions being suspected);
- Possible drug-drug interactions and reactions in special patient groups.

9.1.3.3.1.2. Precedential information:

- information is already included in the summary of product characteristics (SmPC) or patient leaflet;
- a signal has already been assessed by a competent authority in a PSUR or RMP, or was discussed at the level of a scientific expert committee or has been subject to a regulatory procedure.

As a rule, signals not mentioned above should be validated. However, already known signals may need validation if there are suspected differences in frequency, persistence duration, severity or outcome (e.g. fatality revealed) as compared with data/characteristics included into the instruction for medical use or previously reviewed by the competent authority.

9.1.3.3.1.3. Availability of other relevant sources of information providing a richer set of data on a certain adverse reaction:

- literature findings regarding similar reports;
- experimental findings or biological mechanisms;
- Screening of larger databases (combined databases of competent authorities of Member States).

9.1.3.3.2. A signal acquires the status of a validated one, if the process of verification of all documentation concerned evidences suspected new causal relation or a new aspect of the well-known relation and, consequently, is the rationale of further assessment.

9.1.3.3.3. Signals for which the validity of a suspected new causal relation or a new aspect of the known interrelation is not confirmed may require further analysis, e.g. in case of insufficient documentation for a corresponding event of adverse reaction. In such scenarios,



new reports of the adverse reaction or follow-up results of previously received cases from post-authorization period should be reviewed at appropriate time periods to ensure that all relevant reports are considered and reviewed.

9.1.3.3.4. MAHs and competent authorities of Member States should establish tracking systems to capture the results of signal validation including considering and tracing the reasons why signals were not validated as evidencing of an assumed new casual relation or a new aspect of the known interrelation as well as information that would facilitate the search of similar cases and signal validation.

*9.1.3.4. Signal analysis and prioritization*

9.1.3.4.1. A key element of the signal management process is to promptly identify their impact on public health or risk-benefit balance of a medicinal product in treated patients. This prioritization process should include:

a) the strength of evidence and consistency of information, e.g., biological plausibility, a high number of evidential cases reported in a short period of time, the high disproportionality coefficient and increment over time, identification of the signal in various real-life settings (e.g. general practice and hospital settings), sources or countries of signal origin;

b) Impact on patients depending on severity, reversibility, potential for prevention and clinical outcome of an adverse reaction, results of treatment termination in relation to the course of disease and other therapeutic indicators;

c) The public health impact, depending on the extent of exposure to medicinal product of general patient population and groups at-risk (e.g. medicinal products used by pregnant women, children or the elderly) and the way medicinal product is used (e.g. misuse or off-label use). The public health impact may include estimation of the number of patients that may be affected by a serious adverse reaction and this number should be considered in relation to the general population, patients with a target disease and treated patient group;

d) Increased frequency or severity of a known adverse effect;

e) Novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction occurs shortly after a new medicinal product is induced to medical practice;

f) if a marketing authorization application for a new active substance is still under review in the national competent authority and a safety signal is received from a third country where this medicinal product has been already authorized or in any adverse reaction database a severe adverse reaction from a third country was discovered, this signal should be also considered.

9.1.3.4.2. In some circumstances, priority of evaluation can be given to signals received for medicinal products or events with potential high media and pharmacovigilance stakeholder

interest in order to communicate the result to the public and healthcare professionals as early as possible.

9.1.3.4.3. The result of signal prioritization process should include a recommendation of the time frames for signal evaluation.

9.1.3.4.4. The result of the signal prioritization process should be entered in the tracking system, with the justification for the priority attributed.

*9.1.3.5. Signal assessment*

9.1.3.5.1. The objective of signal assessment is to study the evidence of causal relationship of an adverse reaction and suspected medicinal product to quantify the interrelation (preferably in absolute values) and to determine the necessity of collecting additional data or taking regulatory measures. An assessment consists in thorough pharmacological, medical and epidemiological examination of all available information on a relative signal. This review should include the available pharmacological, non-clinical and clinical data and be as complete as possible regarding the sources of information, including the application dossier and the follow-up changes, literature articles, spontaneous reports, and unpublished information held by MAHs and national competent authorities of Member States. Also recommendations from outside experts should be taken into account. When information is drawn from a range of sources, the strengths and limitations of each source should be considered in order to assess the contribution into the safety concern assessment. Summarizing information from different sources also requires the choice of an internationally agreed terminology of medical events. If no such terminological definition exists, an operational definition should be developed.

9.1.3.5.2. Signals may need to be assessed at the therapeutic level or System organ class or at the level of Standardized medical queries in a medical dictionary MedDRA. The search for information may need to be extended to other medicinal products of the same class and to other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of a reaction (e.g. QT prolongation) or to clinical complications of the corresponding adverse reaction (e.g. dehydration or acute renal failure).

9.1.3.5.3. The collection of information from different sources may take some time. To optimize the process the step-by-step method of signal assessment may be used. As for a new signal of a severe adverse reaction temporary measures may be taken, if eventually the first step of assessment based on available information supports the conclusion that there is a potential risk that needs to be prevented.

*9.1.3.6. Recommendation for actions of competent authorities of Member States*

9.1.3.6.1. Assessment finding recommendations may vary according to the applicable

legislation and signal assessment findings.

Although the recommendation takes place after signal assessment based on cumulative information, the need for action should be considered throughout the signal management process defining the justification and expediency of earlier risk minimization actions.

9.1.3.6.2. Response to signal assessment findings may include additional study or risk minimization actions, if the mechanisms of the suspected adverse reaction occurrence point at the possibility of prevention or lowering the severity of the adverse reaction. If findings are based on limited information, it may be required to conduct post-authorization safety study to examine the potential safety issue/concern.

9.1.3.6.3. If a competent authority requests an MAH to take additional measures, the request should specify a time frame by which they should be completed, including provision of progress reports and interim results, proportionate to the severity and public health impact of the safety issue. An MAH and competent authorities of Member States should take into account the possibility of conducting a study within the set time frames with regard to the parameters of the studied safety concern, e.g. frequency of occurrence and need in prospective design of the study. The temporary measures for the provision of the safety and efficient use of a medicinal product or risk elimination including the possibility of the temporary suspension of the validity of the marketing authorization for a medicinal product should be taken into account.

9.1.3.6.4. If there is no risk for patients, a competent authority may take a decision that there is no need in further assessment or further actions.

#### *9.1.3.7. Information exchange*

9.1.3.7.1. A possibility should be provided to exchange information between competent authorities of Member States, MAHs and other parties to communicate information on signals, collect additional data, further assessment of a safety concern and take decisions on patients' health protection. Temporary requirements for information exchange may vary depending on a safety concern, but information should be translated immediately after a signal is rated as valid.

9.1.3.7.2. MAHs should communicate all relative information on signals to the competent authorities of Member States (as part of obligations on pharmacovigilance and the monitoring of the risk-benefit balance of a medicinal product). Validated signals which may have impact on public health and the risk-benefit balance of a medicinal product must be immediately reported to the competent authorities of Member States and in relative cases possible action proposals should be submitted.

9.1.3.7.3. Competent authorities of Member States forward signal assessment findings to MAHs.

#### *9.1.4. Quality requirements*

#### *9.1.4.1. Tracking*

All validation, prioritization, assessment, time frames, decisions, actions, plans, reporting as well as all other key procedures should be recorded appropriately and tracked periodically. Tracking systems should be used for documentation and should also include signals, for which the validation process conducted was not suggestive of a new potentially causal relation or a new aspect of a known relation as they attract special attention in the case of the follow-up analysis. All records need to be archived in accordance with the effective procedures.

#### *9.1.4.2. Quality systems and documentation*

9.1.4.2.1. An essential feature of a signal management system is that it is clearly documented to ensure that the system functions properly and effectively, that the responsibilities and required actions are standardized, that these actions are conducted by people with appropriate qualification and are clear to all parties involved and that there is provision for appropriate control and, when needed, improvement of the system. Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to all signal management processes. Detailed procedures for this quality system should be developed, documented and implemented. The organizational roles and responsibilities for the activities and maintenance of documentation, quality control and review, and for ensuring corrective and preventive actions need to be assigned in-company and recorded. This should include the responsibilities for quality assurance auditing of the signal management system, including auditing of sub-contractors who perform any works in this field. Data and document confidentiality, its security and validity (including integrity when transferred) should be guaranteed.

9.1.4.2.2. Through their tracking system, all parties should keep an audit trail of their signal management activities and of the relevant queries and their outcomes. Information received, search, search findings, evaluation and decisions (positive and negative) on potential signals and also signal test findings should be archived. The data should include signal validation findings.

9.1.4.2.3. The examination of documentation of the MAHs may be requested to demonstrate compliance with these provisions before and after registration procedure to assess the activity performed or inspect.

#### *9.1.4.3. Training*

Staff should be specifically trained in signal management activities in accordance with their functions and responsibilities. The process may include not only the pharmacovigilance staff, but as well the staff that may become aware of potential signals or that participate in the

signal management process, e.g. legal department staff, and staff of pre-clinical, medical, pharmacoepidemiological and marketing studies. Training should include the terminology and available databases with signal sources. The training system procedures and location of the training records should be properly documented, and curricula vitae of specialists and job descriptions should be archived.

## **9.2. Roles and responsibilities**

### ***9.2.1. Roles and responsibilities of competent authorities of member state.***

Competent authority of member state:

- Shall monitor data available within its territory including data received from other sources specified in sub-section 1.1;
- Shall perform validation and other stages of managing signals received from available sources;
- Shall transfer signals that were validated and assessed to relative expert national committees to determine the expedience of further actions for further examination or risk minimization.
- Shall inform other competent authorities of Member States of the EAEU member-states on the identified signals which underwent validation and the measures developed.

### ***9.2.2. Roles and responsibilities of an MAH***

Marketing authorization holder:

- Shall control all available signal data and information;
- Shall monitor all emerging data in databases and perform the international signal detection; the signal detection should include their validation with regard to the components of submitted information set forth in section 1.3.3;
- Shall perform the validation of all detected signals and inform of them to relative competent authorities of Member States;
- Shall notify the competent authorities of Member States, should an urgent safety concern be identified as a result of signal detection activity;
- Shall cooperate with a competent authority in fulfilling signal assessment procedures by way of submitting additional information on request;
- Shall provide the availability of auditing trail in all signal identification procedures.

### ***9.2.3. Processes of the follow-up regulation***

If a competent authority takes a decision on the necessity of additional actions, a signal is assessed and the follow-up actions are agreed upon in relation to marketing authorization

within the time frames proportionate to the severity and seriousness of a safety concern. By the results of the procedures the following decisions may be taken:

- Additional assessment or actions are not needed;
- MAH should conduct an additional assessment of data and submit the results of such an assessment according to the established time frames;
- MAH should submit a PSUR with regard to the identified new aspect of a safety profile;
- MAH should finance the post-authorization study in accordance with the agreed protocol and submit the final findings of such a study;
- MAH should submit a risk management plan or its renewed variant;
- MAH should take measures required for providing a safety and efficient use of a medicinal product;
- The marketing authorization status is subject to alteration; the validity of a marketing authorization should be suspended, recalled or not to be extended;
- Urgent safety restrictions should be imposed;
- For cause inspection of the pharmacovigilance system should be conducted to confirm that MAH follows legislative requirements to the pharmacovigilance system.
- The suspected medicinal product should be included into the list of production which is to be monitored additionally.

#### ***9.2.5. Transparency***

The EAEU member-states should control the expediency of providing general public with important information on safety concerns identified by the pharmacovigilance system by publications on the web-portal and with other available information dissemination tools.

## **10. POST-AUTHORIZATION SAFETY STUDIES**

### **10.1. Introduction**

A post-authorization safety study (hereinafter - PASS) of a medicinal product may be initiated, managed, or financed by a marketing authorization holder voluntarily, or pursuant to an obligation imposed by competent authorities of Member States as a condition for the granting of a marketing authorization, or after the granting of a marketing authorization if it is presumed that risks might exist associated with an authorized medicinal product and requiring further investigation by means of studies.

A PASS may be a clinical trial or a non-interventional study.

### **10.2. Structures and processes**

#### ***10.2.1. Scope***

The requirements of this section apply to non-interventional PASS, which are initiated, managed, or financed by a marketing authorization holder and conducted in the territory of a Eurasian Economic Union member state voluntarily, or pursuant to an obligation imposed by a member state authorized body. PASS involves studies that collect information from patients and healthcare professionals, as well as those that make secondary use of data previously obtained for a different purpose and stored in medical records of patients or other (including electronic) data storage systems.

If a PASS is a clinical trial, its conduct should comply with requirements stipulated by the Union bodies legislative acts and the member states legislation with regard to interventional clinical studies organization and conduct.

### **10.3. Terminology**

The following terminology is used in this section which defines the following:

**“date at which a study commences”** - date of the start of data collection;

**“start of data collection”** - the date from which information on the first study subject is first recorded in the study form (dataset) or, in the case of secondary use of data, the date from which data extraction starts;

**“end of data collection”** - the date from which the analytical dataset is completely available.

### **10.4. General principles**

The principal objective of a non-interventional PASS is to obtain scientific evidence

with potential clinical importance or importance for public health. Such studies should not be conducted if their conduct helps to promote a medicinal product in a market.

Tasks of a PASS may include:

- to quantify potential or identified risks, for instance, to characterize the incidence rate, estimate the rate in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and factors modifying the effects of a medicinal product;
- to evaluate risks of a medicinal product used for authorized indications in patient populations not studied or insufficiently studied at the pre-authorization stage (for instance, pregnant women, specific age groups, patients with renal or hepatic impairment);
- to evaluate the risks of a medicinal product after long-term use;
- to provide evidence about the absence of risks associated with a medicinal product;
- to assess standard clinical practice patterns of drug prescription that add knowledge regarding the safety of the medicinal product (for instance, indication, dosage, co-medication, medication errors);
- to measure the effectiveness of a risk minimization measures (for instance, investigation of drug utilization aspects, patients and healthcare professionals surveys).

Relevant scientific guidances should be considered by marketing authorization holders for the development of study protocols, the conduct of studies, and the writing of study reports. Member states authorized bodies should also take into consideration current scientific guidelines and methodological standards in pharmacoepidemiology for the evaluation of study protocols and study reports.

For studies that are funded by a marketing authorization holder, including studies developed, conducted, and analyzed fully or partially by investigators who are not employees of the marketing authorization holder, the marketing authorization holder should ensure that the investigators are qualified by education, training, and experience to perform their tasks.

### **10.5. Study protocol**

All post-authorization safety studies must be conducted according to a scientifically based study protocol developed by individuals with appropriate scientific background and experience.

For voluntarily initiated PASS, it is recommended that the marketing authorization holder should submit the study protocol, before the start of data collection, to the authorized body of the member state where the conduct of a post-authorization non-interventional safety study for medicinal product is planned.

For PASS initiated by the marketing authorization holder pursuant to an obligation



imposed by the authorized body of the member state, the marketing authorization holder should ensure submission of the study information, including the study protocol, to the authorized body of the member state that imposed the PASS conduct obligation, before the start of data collection. If a PASS is conducted in other member states territories as well, the respective member states authorized bodies should be notified and provided with a brief description of the study protocol.

In order to ensure compliance of the marketing authorization holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance (QPPV) should be involved in the review and sign-off of study protocols. The pharmacovigilance contact person at national level should be informed of any PASS conducted on the territory of that member state and given a copy of the study protocol.

#### ***10.5.1. Format and contents of the study protocol***

The study protocol should include the following sections:

10.5.1.1. PASS title: informative title including a commonly used term indicating the study design and the investigational medicinal product, substance or drug class concerned, as well as a sub-title with a version identifier and the date of the last version.

10.5.1.2. Marketing authorization holder: name and address of the marketing authorization holder.

10.5.1.3. Responsible parties: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author of the protocol, the principal investigators, coordinating investigators for each country and study sites in which the study is to be performed. A list of all collaborating institutions and investigators should be made available to the member states authorized bodies upon request.

10.5.1.4. Abstract: stand-alone summary of the study protocol including the following sub-sections:

- Study title with subtitles, including the version and date of the protocol and the name and affiliation of the main author of the study protocol;
- Rationale and background;
- Research question and objectives;
- Study design;
- Study population;
- variables;
- Data sources;
- Study (sample) size;
- Data analysis;

- Milestones.

10.5.1.5. Amendments and updates: any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, the dates of each change and a reference to the section of the protocol where the change has been made.

10.5.1.6. Milestones: table with planned dates for the following study milestones:

- Start of data collection;
- End of data collection;
- Study progress report(s);
- Interim report(s) of study results, where applicable;
- Final report of study results.

Any other important timelines in the conduct of the study should be presented.

10.5.1.7. Rationale and background: short description of the safety hazard, the safety profile or the risk management measures that led to the initiation of the study, and short critical review of all available published and unpublished data containing estimation of the respective information or indication of gaps in knowledge that the study is intended to fill. The review may encompass results of relevant animal experiments, clinical studies, population statistics data, and previous epidemiological studies data. The review should cite the findings of similar studies, and the expected contribution of the current study.

10.5.1.8. Research question and objectives: research question that explains how the study will address the issue which led to the study being initiated, as well as research objectives, including any pre-specified hypotheses and main presumptions covering the data or information that should be obtained as a result of that study.

10.5.1.9. Research methods: description of the research methods, including the following:

10.5.1.9.1. Study design: overall research design and rationale for this choice.

10.5.1.9.2. Setting: study population defined in terms of persons, place, time period, and selection criteria. A fair rationale for all inclusion and exclusion criteria and description of their impact on the number of study subjects available for analysis are required. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.

10.5.1.9.3. Variables: outcomes, exposures, and other variables, including measured risk factors, potential result confounding factors, and effect modifying factors, including operational definitions.

10.5.1.9.4. Data sources: strategies and data sources for determining exposures, outcomes, and all other variables relevant to the study objectives, such as potential result confounding factors and effect modifying factors. Where the study will use validated data sources, instruments, and measurements, any information on the validation method should be reported. If data collection methods or instruments are tested in a pilot study, the plans for the pilot study should be presented. Involvement of any expert committees and assessment procedures to validate diagnoses should be provided. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, the search strategy and processes, as well as any methods for confirming data from investigators, should be described.

10.5.1.9.5. Study size: any projected study size, precision sought for study estimates, and calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.

10.5.1.9.6. Data management: data management and statistical programmes and hardware to be used in the study procedures for data collection, retrieval and preparation.

10.5.1.9.7. Data analysis: the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorize, analyze, and present results, and procedures to control sources of bias and their influence on results; any statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and any sensitivity analyses.

10.5.1.9.8. Quality control: description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, storage of records and archiving of statistical programmes, description of available validation data for record verification procedures and validation of endpoints. As appropriate, certification and / or qualifications of any supporting laboratory or research groups should be included.

10.5.1.9.9. Limitations of the research methods: any potential limitations of the study design, data sources, and analytical methods, including issues relating to confounding, bias, generalizability, and random error. The likely success of efforts taken to reduce errors should be discussed.

10.5.1.10. Protection of study subjects: safeguards in order to comply with member state legislation requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

10.5.1.11. Data management and reporting of adverse events and adverse reactions:

procedures for the collection, management, and reporting of individual cases of adverse reactions and of any new information that might influence the evaluation of the benefit - risk balance of the medicinal product while the study is being conducted.

10.5.1.12. Plans for disseminating obtained data and communicating study results, including any plans for submission of progress reports, final reports, and publications.

10.5.1.13. References.

This section may also include any additional or complementary information on specific aspects not previously addressed (for instance, questionnaires, case report forms).

Feasibility studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medical events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol along with a summary of their methods and results. Feasibility studies that are part of the research process should be fully described in the protocol (for example, a pilot evaluation of the questionnaire used for patients).

#### ***10.5.2. Monitoring of amendments to the study protocol***

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way, including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, the study shall subsequently be conducted in accordance with international agreements and legal documents that constitute the Union law and the member states legislation.

For voluntarily initiated PASS, it is recommended that the marketing authorization holder should submit the amended or updated study protocol to the authorized body of the member state where the post-authorization non-interventional safety study for the medicinal product is being conducted.

For PASS initiated by the marketing authorization holder pursuant to an obligation imposed by the authorized body of the member state, the marketing authorization holder should ensure submission of information concerning any significant changes made in the study protocol to the authorized body of the member state that imposed the obligation to conduct a PASS, before they are introduced.

### **10.6 Reporting of pharmacovigilance data to the member states authorized bodies.**

#### ***10.6.1. Data relevant to the benefit - risk balance of the medicinal product***

The marketing authorization holder shall monitor the data generated while the study is

being conducted and consider their implications for the benefit – risk balance of the medicinal product concerned. Any new information that may affect the benefit – risk balance of the medicinal product should be communicated immediately to the authorized bodies of the member states in which the PASS is being conducted and in which the medicinal product in question is authorized. Information that might affect the benefit – risk balance of the medicinal product may include that arising from an analysis of information on suspected adverse reactions or results of interim analysis of aggregated safety data.

This communication should not affect information on the results of studies, which should be provided by means of periodic safety update reports (PSURs) and in updates of the risk management plan, if applicable.

#### ***10.6.2. Suspected adverse reactions and other safety information subject to expedited reporting***

Information concerning serious unexpected adverse reactions and other safety information is subject to expedited reporting to authorized bodies of the member states in accordance with the provisions of Good Clinical Practice of the Eurasian Economic Union. Procedures for the collection, management (including a review and assessment by the marketing authorization holder if appropriate), and reporting of suspected adverse reactions should be put in place at the sites conducting the clinical studies and summarized in the study protocol.

#### ***10.6.3. Study reports***

##### ***10.6.3.1. Interim reports***

Interim reports for a PASS being conducted for medicinal products authorized in the member states territories may be requested by the member state authorized body. Requests for interim reports may be made before the study commences or at any time during the study conduct. They may be guided by the communication of efficacy and (or) safety profile-related information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the medicinal product.

The timing of the interim reports should be agreed with the relevant member states authorized bodies and specified in the study protocol. PASS study progress should also be reported in any periodic safety update reports (PSURs) and in risk management plan updates, where applicable.

The contents of the interim report should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients, or number of patients

presenting the monitored outcome, problems encountered during the study conduct and deviations from the expected plan. After review of the report by the member states authorized body, additional information may be requested.

#### 10.6.3.2. *Final study report*

The final PASS report should be submitted to the member states authorized bodies as soon as possible after completion, within 12 months of the end of data collection. The marketing authorization holder should submit the final PASS report to the authorized bodies of the member states where the study is being conducted.

For voluntarily initiated PASS, it is also recommended that the marketing authorization holder should present the final study protocol to the authorized bodies of the member states where the medicinal product in question is authorized.

For PASS initiated by the marketing authorization holder pursuant to an obligation imposed by the member state authorized body, unless a permission for the deviation from the requirements has been presented, the final study report, including an abstract for publication, should be submitted by the marketing authorization holder within 12 months of the end of data collection.

If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

The final study report should include the following sections and information:

10.6.3.2.1. Title: title including a commonly used term and indicating the study design, sub-titles with the date of the final report, name and affiliation of the main author of the study report.

10.6.3.2.2. Abstract: stand-alone summary in the format presented below.

10.6.3.2.3. Marketing authorization holder: name and address of the marketing authorization holder.

10.6.3.2.4. Investigators: names, titles, academic degrees, addresses and affiliations of all main responsible parties, as well as a list of all collaborating institutions and study sites.

10.6.3.2.5. Milestones: planned and actual dates for the following milestones of the study:

- Start of data collection;
- End of data collection;
- Study progress report(s) requested by the member state authorized body;
- Interim report(s) of study results, where applicable;
- Final report of study results;
- Any other important milestones applicable to the study, including the date of protocol

approval by an Ethics Committee if applicable, and the date of study registration in the electronic studies register.

10.6.3.2.6. Rationale and background for study conduct: short description of the safety concern that led to the study being initiated, as well as short critical review of all available published and unpublished data evaluating pertinent safety information or gaps in safety knowledge that the study is intended to fill.

10.6.3.2.7. Research question and objectives: research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.

10.6.3.2.8. Amendments and updates: list of any substantial amendments and updates to the initial study protocol after the start of data collection, including a justification for each amendment or update.

10.6.3.2.9. Research methods including:

- Study design: key elements of the study design and the rationale for design choice.
- Setting: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up and data collection, in case of a systematic review or meta-analysis - study characteristics used as criteria for eligibility, with rationale.

- Subjects: any target population and eligibility criteria of study subjects. Sources and methods of selection of participants should be provided, including, where relevant, methods for case ascertainment, as well as number of and reasons for dropouts.

- Variables: all outcomes, exposures, predictors, potential result confounding factors, and effect modifying factors, including operational definitions. Diagnostic criteria should be presented if applicable.

- Data sources and measurement: for each variable of interest, sources of data and details of methods of assessment and measurement (if applicable) should be provided, as well as a comparison of methods used for the assessment (if more than one method is used). If the study has used an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, a description of all information sources, search strategy, methods for selecting studies, methods of data extraction, and any processes for obtaining or confirming data from investigators should be provided.

- Bias: a description of the actions or measures taken to handle potential sources of bias.

- Sample size: sample size, rationale for any sample size calculation and any method for attaining the projected sample size.

- Data transformation: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

- Statistical methods: description by the following aspects:
  - main summary measures;
  - all statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies;
  - any methods used to examine subgroups and interactions;
  - how missing data were addressed;
  - any sensitivity analysis;
  - any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.

- Quality control: mechanisms and procedures to ensure data quality and integrity.

10.6.3.2.10. Results: presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals. This section should include the following sub-sections:

- Participants: numbers of study subjects at each stage of the study (for instance, numbers potentially eligible, screened for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed, and reasons for non-participation at any stage). In the case of a systematic review or meta-analysis - number of studies screened, assessed for eligibility, and included in the review with reasons for exclusion at each stage.

- Descriptive data: characteristics of study participants, information on exposures and potential confounders and number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis - characteristics of each study from which data were extracted (for instance, sample size, follow-up);

- Outcome data: numbers of participants across categories of main outcomes;

- Main results: unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (for instance, 95 % confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period;

- Other analyses: other analyses done, for instance, analyses of subgroups and interactions, as well as sensitivity analyses;

- Adverse events and adverse reactions: data management and submission of information concerning adverse events and adverse reactions to the member states authorized



bodies. For certain study designs, such as case-control or retrospective cohort studies, particularly those involving electronic health care records, systematic reviews and meta-analyses where it was not feasible to make a causality assessment at the individual case level, this should be stated.

#### 10.6.3.2.11. Discussion:

- Key results: key results with reference to the study objectives, prior research in support of or conflicting with the findings of the completed post-authorization safety study, and, where relevant, impact of the results on the benefit - risk balance of the medicinal product.

- Limitations: limitations of the study taking into account circumstances that may have affected the quality and integrity of the data, limitations of the approach and methods used to minimize their impact (for instance, missing or incomplete data, imputations applied), sources of potential bias, and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed.

- Interpretation: interpretation of study results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

- Generalizability: the generalizability (external validity) of the study results.

#### 10.6.3.2.12. References.

#### 10.6.3.2.13. Other information: any additional or complementary information on specific study aspects not previously addressed.

*10.6.3.3. The abstract of the final study report should include a summary of the study methods and findings presented in the following format:*

- Title, with subtitles, including the date of the abstract and the name and affiliation of the main author;

- Key words (not more than five keywords indicating the main study characteristics);

- Rationale and background;

- Research question and objectives;

- Study design;

- Setting;

- Subjects and sample size;

- Variables and data sources;

- Results;

- Discussion (including, where applicable, an evaluation of the impact of study results on the benefit -risk balance of the medicinal product);

- Marketing authorization holder;
- Name and affiliation of the principal investigator.

### **10.7. Publication of study results by authors**

For studies that are fully or partially conducted and analyzed by investigators who are not employees of the marketing authorization holder, the marketing authorization holder is recommended to agree in advance with the principal investigator a publication policy. It is recommended that the publication strategy should allow the principal investigator to independently prepare publications based on the study results irrespective of data ownership. In this case, the marketing authorization holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication, avoiding unjustified delays in publication. Any requests for changes in the manuscript should be scientifically justified. The marketing authorization holder should be given a right to request removal of any confidential information.

#### ***10.7.1. Submission of study results publications to the member states authorized bodies***

It is recommended that the marketing authorization holder should communicate to the authorized bodies of member states, in which the medicinal product is authorized, the manuscript of the article within two weeks after acceptance for publication.

### **10.8. Data protection**

Marketing authorization holders and investigators shall follow relevant legislation of the member states in which the study is being conducted, for the personal patient data protection. The marketing authorization holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation, and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.

### **10.9. Quality systems, audits and inspections**

The marketing authorization holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected, and verified. Any change in the data should be recorded to ensure traceability. The marketing authorization holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

**10.10. Impact on the risk management system**

Non-interventional PASS (and, in general, any interventional or non-interventional post-authorization safety study) conducted to investigate a safety concern as described in RMP should be described in the RMP. The study protocol should be provided as an appendix to the RMP.

If an RMP is absent, a new RMP should be developed that should contain data from the post-authorization safety study. Appropriate changes should be made in all respective sections and modules of the RMP, with consideration given to the study conduct, including the safety specification, the pharmacovigilance plan, and the risk minimization plan, as well as the review of risk minimization measures.

**10.11. Procedure for mandatory post-authorization safety studies**

In the member states, conducting a post-authorization safety study (PASS) may be mandatory for the evaluation of a primary marketing authorization application or at the post-authorization stage, if there is any concern in relation to the safety profile of an authorized medicinal product (a sound expert opinion on absence of important safety data which characterize medicinal safety profile and which production requires active methods of safety investigation due to inability to perform such investigation or safety risk(s) evaluation with routine pharmacovigilance methods). This authorized body's requirement should be justified in an appropriate manner by data from a safety and efficacy profile assessment; it should be prepared in writing and include objectives and timelines for submission and conduct of the study. This requirement may also include recommendations concerning key characteristics of the study (for instance, study design, settings, impact, outcomes, target population). Recommended methods may include active surveillance techniques (for instance, monitoring at certain clinical centres, prescription monitoring, registries), comparative observational non-interventional studies (for instance, cohort studies (monitoring), case – control studies, case series studies, etc.), clinical trials, drug utilization studies, and pharmacoepidemiological studies.

Within 30 calendar days since receipt of the written member state authorized bodies notification on obligation on PASS at post-authorization stage the marketing authorization holder may ask to be permitted to submit written observations on medicine safety as a PASS. The member states authorized bodies define the time frame for the period for submission of such observations. On the basis of written observations submitted by the marketing authorization holder, the member states authorized bodies should revoke or confirm this obligation.

## **10.12. Control over non-interventional post-authorization safety studies**

### ***10.12.1. Roles and responsibilities of the marketing authorization holder***

The marketing authorization holder is responsible for ensuring that the study meets the criteria of a non-interventional study.

The marketing authorization holder responsible for the PASS should ensure fulfilment of its pharmacovigilance commitments, as well as opportunities for its audit, inspection, and verification.

### ***10.12.2. Competent bodies of the Member States***

Following decision of the member states authorized bodies an obligation to conduct a non-interventional PASS, the marketing authorization holder should develop a study protocol and submit it to the member state authorized body for review. Within 60 days from submission of the draft protocol, the national competent authority shall issue a response:

- endorsing the draft protocol;
- recommending necessary changes to the study protocol;
- objecting the study protocol;
- notifying the marketing authorization holder that the study is a clinical trial falling under the scope of international agreements and legal documents that constitute the Union law and the member states legislation in respect to clinical research conduct.

The letter of objection shall set out in detail the grounds for the objection in any of the following cases:

- if it is considered that the conduct of the study promotes the use of a medicinal product; and
- if the design of the study does not fulfil the study objectives.

The study may be initiated only after a written approval of the study protocol is issued by the member state authorized body.

After the start of the study, any significant changes in the study protocol should be submitted to the member state authorized body before these changes are introduced. The member state authorized body should perform an assessment of the changes and notify the marketing authorization holder of their approval or rejection within 30 days of submission.

Upon completion of the study, the marketing authorization holder shall submit a final study report, including an abstract for publication, to the member state authorized body as soon as possible and not later than 365 calendar days (12 months) after the end of data collection, unless a written waiver for deviating from the report submission time frame requirements has been granted by the member state authorized body. The member state authorized body shall

review the final study report and subsequently provide the marketing authorization holder with the results of the report's assessment, which may include additional questions that the marketing authorization holder will have to answer. Based on the results of the report review and assessment of the potential effects of the obtained data on the benefit - risk balance of the medicinal product, the member state authorized body should determine if there is any need for recommendations for making changes in the regulatory status of the medicinal product, its administration, or determine the necessity for any other appropriate measures in order to ensure a favorable benefit - risk balance for the use of the medicinal product.

## 11. SAFETY COMMUNICATION

### 11.1. Structures and processes

#### 11.1.1. Objectives of safety communication

Safety communication aims at:

- a) providing timely, evidence-based information on the safe and effective use of medicines;
- b) facilitating optimization to healthcare practices (including self-medication practices) where necessary;
- c) changing approaches, set practice and behaviors in relation to the use of medicinal products;
- d) supporting risk minimization behavior ;
- e) facilitating informed decisions on the rational use of medicines.

In addition to the above effective, high quality safety communication can support public confidence in the regulatory system.

#### 11.1.2. Principles of safety communication

The following principles of safety communication should be applied:

- The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process. This element should be part of risk assessment.
- There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (i.e. competent authorities, other public bodies and marketing authorization holders).
- Safety communication should deliver relevant, clear, accurate and consistent messages and reach the target audiences at the right time for them to take appropriate action.
- Safety communication should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.
- Information on risks should be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and, if available, expected time to recovery.
- Safety communication should address the uncertainties related to a safety concern. This is of particular relevance for emerging information which is often communicated while competent authorities are performing their evaluations; the usefulness of communication at this

stage needs to be balanced against the potential risk of confusion if uncertainties are not properly clarified.

- Information on competing risks such as the risk of non-treatment should be included where appropriate.

- The most appropriate quantitative measures should be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; for risk comparisons, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the benefit-risk balance may also be used.

- Patients and healthcare professionals should, where possible, be consulted and messages pretested early in the preparation of safety communication, particularly on complex safety concerns.

- Where relevant safety communication should be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations (if required)

- The effectiveness of safety communication should be evaluated where appropriate and possible.

- Safety communication should comply with relevant requirements relating to individual data protection.

### ***11.1.3. Target audiences***

The primary target audiences for safety communication issued by competent authorities of Member States and marketing authorization holders should be patients and healthcare professionals who use medicinal products.

As primary target audiences, healthcare professionals play an essential role. Effective safety communication enables them to perform pharmacological therapy taking into consideration the most actual safety information and recommendations and to give clear and useful information to their patients, thereby promoting patient safety and confidence in the regulatory system.

The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on medicines. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from the competent authorities in addition to the information they receive from other sources, such as from the marketing authorization holders.

### ***11.1.4. Content of safety information***

Taking into account the principles in 11.1.2., safety information should contain:

- a) important emerging information on any authorized medicinal product which has an impact on the medicine's benefit-risk balance under any conditions of use;
- b) the reason for initiating safety communication clearly explained in a form clear to the target audience;
- c) necessary recommendations to healthcare professionals and patients related with a safety concern communicated;
- d) when applicable, a statement on the agreement between the marketing authorization holder and the competent authority on the safety information provided;
- e) information on any proposed change to the product information (e.g. the summary of product characteristics or package leaflet);
- f) a list of literature references, when relevant or a references to the sources where more detailed information on safety aspect communicated can be found;
- g) where relevant, a reminder of the need to report suspected adverse reactions to the national competent authorities by means of national spontaneous reporting systems.

The information in the safety communication shall not be misleading and shall be presented objectively. Safety information should not include any material or statement which might constitute advertising or other information aimed at the product promotion.

#### ***11.1.5. Means of safety communication***

The use of whole increasing variety of information transfer means should be considered when issuing safety communication in order to reach the target audiences and meet their growing expectations. Different communication tools and channels of the information transfer which can be used are discussed below in sections 11.1.5.1.-11.1.5.5.

##### ***11.1.5.1. Direct healthcare professional communication***

A direct healthcare professional communication is defined in this document as a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorization holder or a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product according to new safety data. A direct healthcare professional communications are not replies to enquiries from healthcare professionals, nor are they meant as educational material for routine risk minimization activities.

The preparation of informative material for direct healthcare professional communication involves cooperation between the marketing authorization holder and the competent authorities. The marketing authorization holder should receive approval from the respective competent authority of the Member State of EAEU concerning the informative



material content for direct healthcare professional communication. Agreement between the competent authority and the marketing authorization holder should be reached before informative materials are issued by the marketing authorization holder. The competent authority's approval should be obtained concerning the content and communication plan including the target audience and schedule of information communication.

The marketing authorization holder should provide not less than two working days to comment on the remarks from the competent authority concerning informative material and communication plan.

When necessary and as applicable, more time should be granted for this procedure at the discretion of the competent authority, the timelines can be adapted taking into consideration the situation urgency.

Where there are several marketing authorization holders of the same active substance for which information for direct healthcare professional communications is to be issued, a single consistent message should normally be delivered.

Whenever possible, it is advised that healthcare professionals' organizations or learned societies are involved as appropriate during the preparation of information for direct healthcare professional communications to ensure that the information they deliver is useful and adapted to the target audience.

*11.1.5.1.1. A direct healthcare professional communication may be an additional risk minimization measure as part of a risk management plan.*

A direct healthcare professional communication should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicinal product:

- suspension, withdrawal or revocation of a marketing authorization due to changes in safety profile;
- an important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to changes in safety profile;
- a restriction in availability or discontinuation of a medicinal product manufacture with potential detrimental effects on patient care.

*11.1.5.1.2. Other situations where dissemination of a direct healthcare professional communication should be considered are:*

- new major warnings or precautions for use in the product information ;
- new data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- substantiated knowledge that the medicinal product is not as effective as previously

considered;

- new recommendations for preventing or treating adverse reactions or to avoid misuse or medication error with the medicinal product;

- ongoing assessment of an important potential risks, for which data available at a particular point in time is insufficient to take regulatory action (in this case, the direct healthcare professional communication should encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimize the potential risk).

A competent authority have the right to disseminate the information for direct healthcare professional communication or to request the marketing authorization holder to prepare, agree and disseminate the information for direct healthcare professional communication in any situation where the competent authority considers it necessary for the continued safe and effective use of a medicinal product.

The competent authorities are enabled to publish final variant in informative material for direct healthcare professional communication. When necessary, the competent authorities can issue an additional safety report and disseminate the informative material among organizations and healthcare professionals.

#### *11.1.5.2. Information for non-specialists*

Communication material in lay language (i.e. for non-professional) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. Lay language documents should contain the competent authority's recommendations and advice for risk minimization for patients and healthcare professionals in relation to the safety concern, and should be accompanied by relevant background information.

Competent authorities publish lay language documents on their national medicines web-portals and may additionally disseminate them to relevant parties such as patients and healthcare professionals' organizations.

Whenever possible, it is advised that patients and healthcare professionals are involved during the preparation of lay language documents to ensure that the information they deliver is useful and adapted to the target audience.

#### *11.1.5.3. Press communication*

Press communication includes press releases and press briefings which are primarily intended for journalists.

Competent authorities may send press releases directly to journalists in addition to publishing them on their websites that will ensure that journalists receive information that is consistent with the competent authority's scientific assessment. Interaction with the media is an

important way to reach out to a wider audience as well as to build trust in the regulatory system.

Marketing authorization holders may also prepare and publish press releases which reflect the position of the marketing authorization holder on a safety topic but they should make reference to any regulatory action taken by the competent authority. Relevant ongoing reviews should be mentioned in any communication by the marketing authorization holder.

Although aimed at journalists, press releases will be read by other audiences such as healthcare professionals, patients and the general public; therefore, reference should be made to related communication materials on the topic. In cases where a direct healthcare professional communication is also prepared, healthcare professionals should receive it prior to or around the same time of the publication or distribution of a press release make healthcare professionals prepared to respond to patients.

Press briefings with journalists should be considered by competent authorities for safety concerns or other matters relating to the safety of medicinal products that are of high media interest or when complex or public-health-sensitive messages need to be conveyed.

#### *11.1.5.4. Website*

A website is a key tool for members of the public (including patients and healthcare professionals). Competent authorities as well as marketing authorization holders should ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up-to-date, with any information that is out-of-date marked as such or removed.

#### *11.1.5.5. Other web-based communications*

Online safety information may also be disseminated via other web tools. When using newer, more rapid communication channels, special measures should be taken to ensure that the accuracy of the information released is not compromised. Communication practices should take into account emerging communication tools used by the various target audiences.

#### *11.1.5.6. Bulletins and newsletters*

Bulletins and newsletters are intended to provide at regular intervals new information about medicinal products and their safety and effectiveness. Competent authorities can reach a large audience with these tools by using web-based applications and other available means.

#### *11.1.5.7. Inter-authority communication*

When one competent authority takes regulatory action on a particular safety concern, other competent authorities usually need to respond to enquiries or communicate on the same issue. The use of inter-authority communication materials in the form of documents specifically prepared by a competent authority to assist its partners in responding to external enquires or communicating on a specific safety issue.

#### *11.1.5.8. Responding to enquiries from the public*

Competent authorities and marketing authorization holders should have systems in place for responding to enquiries about medicinal products from individual members of the public. Responses should contain the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by competent authorities. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

#### *11.1.5.9. Other means of communication*

In addition to communication tools discussed above, there are other tools and channels for safety communication such as publications in scientific journals and journals of professional bodies.

Some tools and channels may be used in the context of risk management; risk minimization measures often include specific programs for risk communication. Tools used in such programs, such as patient alert cards or healthcare professional safety guidance, are described in more detail in Module 12 of these Guidelines.

#### *11.1.6. Effectiveness of safety information*

Safety information is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience in reaction to the information. Adequate mechanisms should be introduced in order to measure the effectiveness of the communication based on clear objectives (indicators). Measuring effectiveness allows conclusions to be made and helps in making decisions on prioritizing and adapting tools and practices to meet the needs of the target audiences. A research-based approach will normally be appropriate in order to establish that safety information has met the standard of p.11.1.2. of these Guidelines. This approach enables to compare different outcomes, including behavior, attitudes, and knowledge.

The marketing authorization holders should be responsible for evaluating the efficacy of direct healthcare professional communication regarding safety concerns. The marketing authorization holders should inform the competent authorities on the results of assessment of direct communication efficacy and on any difficulties identified (e.g. problems related to the list of recipients or the timing and mechanism of dissemination). Appropriate corrective and preventative actions should be taken in all cases when a lack of efficacy of direct healthcare professional communication has been determined.

#### *11.1.7. Quality system requirements for safety communication*

In accordance with the quality system requirements for safety communication specified in Module 2 of these Guidelines, respective procedures should be in place to ensure that safety

communications comply with the principles in p.11.1.2 of these Guidelines. Performance and documenting of control procedures regarding communication of safety information which a quality control subject should be ensured.

## **11.2. Coordination of safety announcements in the Member States of the EAEU**

### ***11.2.1 Cooperation of the competent authorities in the Member States of the EAEU regarding medicinal products safety communication.***

The competent authorities exchange information concerning safety information planned for publication with regular intervals within communicative cooperation of the competent authorities in the Member States of the EAEU.

#### ***11.2.1.1 Direct healthcare professional communications for safety issues concerning medicinal products in the Member States of the EAEU***

If a medicinal product is registered in more than one Member State of the EAEU, the national competent authorities exchange information relating the content of information for direct healthcare professional communications and communication plan which have been agreed. The national competent authorities share final version of informative material using communication cooperation system.

#### ***11.2.2. Requirements for the marketing authorization holders***

As soon as a marketing authorization holder intends to make a public announcement/public informing/information publication relating to information on pharmacovigilance or safety concerns in relation to the use of a medicinal product concerned, it should inform the competent authorities of the Member States of the EAEU where the medicinal product has been authorized. The information should be submitted to the competent authorities for informing and agreement in advance and under conditions of prohibited publishing within at least 24 hours before publishing. Informing the authorities at the same time as the public should only occur exceptionally and under justified grounds.

The marketing authorization holder is responsible that information which is presented to the public is objective and not misleading.

Whenever a marketing authorization holder becomes aware that a third party intends to issue communication that could potentially impact on the benefit-risk balance of a medicinal product authorized in the Member States of the EAEU, the marketing authorization holder should inform the relevant competent authorities in the Member States of the EAEU.

#### ***11.2.3. Cooperation with third parties***

Third parties (e.g. scientific journals, learned societies, patients' organizations) are encouraged to inform the competent authorities in the Member States of the EAEU of any

relevant emerging information on the safety of medicinal products authorized in the EAEU and, if publication of this information is planned, to share the information with the competent authority ahead of publication.

## **12. RISK MINIMIZATION MEASURES**

### **12.1. Introduction**

Risk minimization measures are interventions intended to prevent or reduce the occurrence of an adverse reactions associated with the exposure to a medicine, or to reduce their severity of adverse reactions or impact on the patient should adverse reactions occur.

Risk minimization measures included in this module shall be considered in the context of the main part of requirements to a risk minimization system (section 6 of these Guidelines).

Risk minimization measures may include routine risk minimization measures or additional risk minimization measures. Routine risk minimization measures shall apply to all medicinal products and are described in detail in section 6 of these Guidelines.

Most safety concerns may be managed as appropriate by routine risk minimization measures, however, routine risk minimization measures may be insufficient for certain risks, and, to ensure proper risk management and/or improve the risk-benefit balance of an authorised medicinal product, additional risk management measures will be necessary.

This section contains guidelines on how additional risk minimization measures should be applied and guidelines on selection of appropriate risk minimization tools.

Risk minimization measures should be determined based on safety concerns presented in a safety specification of medicinal product. Each safety concern should be addressed separately. Following items should be considered when selecting the most appropriate risk minimization measure to be applied: the severity of potential adverse reactions, their preventability or clinical actions required to reduce risk, indications for use, route and mode of administration of the medicinal product, target population and the type of health care institutions where this medicinal product is used.

A safety concern may be addressed by more than one risk minimization measure, and a certain risk minimization measure may apply to more than one safety concern.

The Marketing Authorization Holder is responsible for ensuring proper control of risk minimization measures implementation for measures that are included in a Risk Management Plan approved by competent authorities of Member States or defined as conditions of marketing authorization.

National competent authorities of Member States are responsible for control of risk minimization measures implementation for measures included in a Risk Management Plan or defined as conditions of marketing authorization.

## **12.2. Structures and processes**

### ***12.2.1. General principles***

Risk minimization measures are aimed to ensure safe and efficient use of an approved medicinal product throughout its life cycle. The benefit-risk balance of a medicinal product may be improved by reducing the risk and severity of consequences of adverse reactions, as well as optimizing benefit by way of targeted selection and/or exclusion of patients, or through close monitoring of treatment (e.g., a specific dosage regimen, corresponding laboratory monitoring, follow-up of patients, etc.). Risk minimization measures shall be practical guidelines for optimal use of medicinal product in the routine practice to ensure that right drug is given to right patient in an optimal dose at right time by appropriately trained healthcare specialist that has received information for correct prescription of medicinal product and has skills in disease case management, as well as reliable information and due control.

There is a number of various methods used as additional risk minimization measures. This section of regulation of medicinal product circulation is in constant development, and available methods will be supplemented by new ones, including those including broader use of Internet technologies.

Successful implementation of additional risk minimization measures requires contribution by all involved parties, including Marketing Authorization Holders, patients and health care specialists.

Additional risk minimization measures should have a clearly defined target which is consistent with the general target for minimizing specific risks and/or optimizing benefit-risk balance. Specific targets and predetermined parameters to measure achievement of a set target, with defined milestones shall become guidelines in development of additional risk minimization measures.

Appropriate monitoring should be in place to measure predetermined parameters at the stage of measure introduction, efficiency measurement in the process of and after the completion of implementation should be ensured.

A characteristic of a safety concern in the context of the overall benefit-risk balance of the medicinal product, therapeutic value of the drug, target population and necessary clinical actions for risk minimization are the factors that shall be taken into consideration when selecting tools/methods of risk minimization and defining a strategy of implementation of risk minimization measures to ensure achievement of desired public health protection results. On a regular basis interim assessment of efficiency of implemented risk minimization measures should be performed to timely identify if the measures were of insufficient efficacy and implementation of corresponding corrective measures is required and in place.



A risk minimization plan is a part of a Risk Management Plan. A risk minimization plan shall include the following sections:

- Substantiation of the necessity to introduce additional risk minimization measures (related to certain safety problem): in this section, a substantiation of proposed additional risk minimization measures should include specific targets for each proposed measure. A clear description of how a proposed additional risk minimization measure will aim at a specific safety concern should be given;

- Description of additional risk minimization measures: in this section, a description of selected additional risk minimization measures, including a description of tools/methods that will be used, and key elements of their content shall be provided;

- Execution\implementation plan: in this section, a detailed description of proposals on implementation of additional risk minimization measures shall be provided (e.g., a characteristic of interventions, detailed information on the target audience, a plan of conducting educational programs and/or distribution of educational materials, a mechanism of coordination of these measures with other Marketing Authorization Holders, if applicable);

- Assessment plan: in this section, a detailed plan with milestones of additional risk minimization measures assessment in terms of execution\implementation of the planned process\activities and in terms of overall effect on outcomes (e.g., risk reduction) shall be presented.

#### ***12.2.2. Risk minimization measures***

Additional risk minimization measures should be proposed in cases when they are considered as conditions of safe and efficient use of a medicinal product. Proposed additional risk minimization measures should be scientifically justified, developed and presented by specialist having corresponding qualifications.

Additional risk minimization measures may have various targets, designs, target audiences and complexity. These measures may be used for: selection of appropriate patients in whom the benefit of the drug would prevail over its risk, excluding patients with counter-indications for a medicinal product use; ensuring due treatment monitoring associated with control of significant risks and/or due management of an adverse reaction in case it has developed.

In addition, specific risk minimization measures targeting medication error risk and/or ensuring appropriate prescription of a drug may be developed, when it's not possible to achieve this target only by providing information in the product package insert or on the label.

If a request for additional risk minimization measures is made, justification of the request shall be documented, as well as specific safety concerns shall be named, and detailed

implementation and assessment plan should be provided.

Additional risk minimization measures may include the following:

- educational program;
- controlled access program;
- other risk minimization measures.

#### *12.2.2.1. Educational program*

Many additional risk minimization tools/methods that may be used in educational program are based on target provision of information contained in the package insert and on the product label. Any educational material should be aimed at achieving certain risk minimization targets and should contain clear and specific information.

The target of an educational program should be optimization of medicinal product use through positive influence on actions of health care specialists and patients to minimize risk. Educational materials shall be created based on the assumption that there is simple practical and efficient recommendation for targeted education, and that implementation of this measure is considered important and significant to minimize significant risk and/or optimize benefit-risk balance.

Educational tools used in educational program may have a number of different target audiences, may be aimed at more than one safety concern and may be delivered through a combination of means and mass media (in hard copy, by way of audio, video, Internet, personal training). It is recommended that materials are presented using the entire range of formats to ensure assess, including circumstances of breakdown of an information tool or absence of Internet access.

The content of any educational materials should be fully aligned with current approved medicinal product package insert and product label. Advertising elements, direct or indirect, should not be included in the content of educational material. Educational materials should emphasize risks related to the medicinal product and management of such risks requiring additional risk minimization measures.

Any educational program shall be fully separated from advertising activities, and contact information of doctors and patients that can be received through implementation of educational program, shall not be further used for advertising purposes.

Educational tools described below may be considered individually or in combination during development of an educational program of additional risk minimization.

##### *12.2.2.1.1. Educational Tools*

Educational tools shall have a clearly defined purpose, including unambiguous definition of the risk(-s) in the context of the problem, properties of the risk(-s) and specific

actions to be taken by the healthcare professionals and/or patients for the purpose of minimizing of any such risk(-s).

This information should focus on clearly defined actions pertaining to specific safety concerns in the context of risk minimization and be free of any details that are not directly related to the safety concern and already are properly described in the package insert or label.

Elements of information to be included in educational tools/methods may include:

- a) medicinal product prescription guidelines, including the selection of the patient, control and monitoring aiming to minimize the important risks;
- b) risk management guidelines (for healthcare professionals, patients or care givers);
- c) guidelines on provision of information about the identified adverse reactions that are of special interest to characterize any specific risk.

#### *12.2.2.1.1.1. Educational Tools/Methods for Healthcare Professionals*

The purpose of any educational tool/method for healthcare professionals is representation of specific aspects of the user's guidance (what to do) and/or counter-indications (what not to do) and/or warnings (how to manage the adverse reactions) related to the medicinal product and specific risks requiring the additional risk minimization measures, including:

- selection of patients;
- treatment method, dosage regimen, control and monitoring;
- special administrative procedures or dispensing of the medicinal product; and
- detailed information to be provided to the patients.

Format of the educational tool/method depends on the information that need to be provided, e.g. if making a prescription to an individual patient is to be preceded by a certain number of actions, a checklist appears to be the appropriate format. Format of the brochure may be more appropriate, to facilitate the experts in proper understanding of specific risks with a focus on early detection and control of adverse reactions, whereas posters may contain useful therapeutic guides and outline the ways of taking of the medicinal product. Other formats are an option, depending on the focus, scope of information, target population and other factors.

#### *12.2.2.1.1.2 Educational Tools/Methods for Patients and Caregivers*

Educational tools/methods for the patient shall focus on facilitating the patients or caregivers in understanding of indications and symptoms that are important for early detection of the specific adverse reactions requiring the additional risk minimization measures, as well as optimization of further case management. Whenever appropriate, educational tool/method may be used for provision of information and for reminding the patient about the important actions, e.g. keeping records of the medicinal product dosage or diagnostic procedures that are to be registered or performed by the patient and discussed with the healthcare professionals, so as to

promote the compliance with any stages necessary for efficient application of the medicinal product.

#### *12.2.2.1.1.3 Patient Alert Card*

This tool serves to guarantee that any special information about the treatment of the patient and the associated risks (e.g., potential interaction with other drugs) is always available to the patient and to the relevant healthcare professional. The information should contain mandatory minimum for communication of key instructions regarding the risk minimization measure and the necessary actions to alleviate symptoms under any circumstances, including emergencies. Portability of this tool is a key characteristic.

#### *12.2.2.1.2. Controlled Access Program*

Controlled access program comprises operational measures promoting medicinal product access control beyond the scope guaranteed by the standard risk minimization measures, i.e. regulatory status of the medicinal product. Controlled access should be regarded as a method allowing to minimize serious risks for the medicinal product with proven advantage, which cannot be achieved without the additional risk minimization measures due to the risk of the impact on patient health.

Following requirements (individual or combined with other requirements) listed below should be adhered to prior to the prescription and/or dispensing and/or using of the medicinal product in frames of controlled access program:

- a) specific methods of patient control and/or examination to promote compliance with strictly defined clinical criteria;
- b) physician prescribing the medicinal product, health care professional dispensing the medicinal product, and/or patient should document their receipt and confirm understanding of information about a serious risk associated with application of the medicinal product;
- c) precise procedures outlining the systemic follow-up monitoring of patient by means of registration in the special data collection system, e.g. patients registry;
- d) medicinal products may be obtained only in the properly licensed drug stores.

Requirements to special examination or control of the patient's condition may be used in certain cases as a tool promoting the controlled access, e.g. patient condition monitoring, laboratory findings or any other characteristics (e.g., ECG) prior to and/or in the course of treatment, hepatic function analyses, regular blood tests, pregnancy test (which may be a component of a pregnancy prevention program). Measures shall be taken in order to promote control in accordance with the package insert, whenever it constitutes a clinical factor in the context of the risk-benefit balance of the medicinal product.

#### *12.2.2.1.3. Other Risk Minimization Measures*

#### *12.2.2.1.3.1 Contraception Program\Pregnancy prevention*

Contraception Program is a combination of measures aiming to minimize the risk of impact of the medicinal product with a known or potential teratogenic effect on the fetus during pregnancy. This program shall facilitate introduction of a control mechanism which would make sure that female patients are not pregnant at the beginning of the therapy or do not conceive during the entire therapy course and/or during a certain period following the completion thereof. Contraception Program may also focus on male patients, if the use of a medicinal product by the biological father may have negative impact on the outcome of pregnancy.

Contraception program combines the educational tools and appropriate tools promoting the controlled access to the medicinal product. Therefore, the following elements shall be considered both individually and collectively while planning the contraception program:

a) educational tools focusing on healthcare professionals and patients, to inform them about teratogenic risk and the actions to be taken for its minimization, e.g. guide on using more than one contraception method and various contraceptives; information for the patient concerning the period during which the patient should avoid pregnancy upon completion of the treatment;

b) controlled access at the level of prescription or dispensing of the medicinal product, including mandatory pregnancy test and control of negative results by the healthcare and pharmaceutical professional prior to prescription or dispensing of the medicinal product(-s);

c) maximum effective period of the prescription – 30 (Thirty) calendar days;

d) consultancy in case of unintentional pregnancy and evaluation of the outcome of any accidental pregnancy.

Organization and the design of the pregnancy register that would cover all patients who got pregnant during the treatment or within the relevant period following the completion of treatment (e.g., 3 (Three) months) should be considered.

#### *12.2.2.1.3.2 Direct Healthcare Professionals communication*

Direct contact with healthcare professionals is an active form of informing when safety data are supplied directly to specific healthcare professionals by the Marketing Authorization Holder or by the competent authority, advising on the need for serious actions to be taken or adapting the general medical practices to minimize the risks and/or mitigate the severity of the adverse reactions caused by the medicinal product (see Section 11).

#### **12.2.3. Risk Minimization Procedures**

The additional risk minimization procedures may include active measure(-s) which should be introduced and complied with by a certain target population. Due attention should be

given to the timeframes applicable to risk minimization procedures, including any other procedures promoting the mission within the target group. For example, single implementation of educational tools/methods “before the launch” of the program may prove to be insufficient for provision of information to all potential healthcare professionals who prescribe the medicinal product and/or consumers, including any new healthcare professionals and consumers. There may be a need for additional, periodic re-distribution of the tools/methods after the launch of the risk minimization program. Due attention shall be paid to the overall format of educational tools/methods to promote clear distinction from any kind of advertising/promotional materials. The educational tools shall be submitted to the competent authority for approval separately from advertising material, and the accompanying letter shall specifically point out whether it is about advertising or educational materials. Educational materials should be submitted for regulatory approval, apart from any advertising materials, and they should be specifically marked as non-advertising in cover letter to regulator for such submission. Educational materials should be distributed separately from any advertising materials, educational materials should have a clear statement that these are non-promotional. Quality assurance mechanisms should guarantee that the existing distribution systems fit the target of risk minimization and are properly controlled.

#### ***12.2.4. Efficiency assessment of Risk Minimization Measures***

Efficiency of risk minimization measures should be evaluated for the assessment of efficiency of the active risk minimization measures and revealing the root cause of low efficiency and the need for remedial actions. Efficiency evaluation shall cover each risk minimization measure individually and the entire program.

Efficiency evaluation should be based on various aspects of the ongoing risk minimization measures: the process itself (i.e., progress of the program), impact on awareness and changes in behavior of the target group, and the results (i.e., if predetermined targets of risk minimization were achieved; short term or long term, etc.). Timing to evaluate each aspect of the ongoing measure shall be thoroughly planned in the RMP prior to the launch of the relevant measures.

Efficiency evaluation shall be based on the two groups of indicators:

- process indicators and
- result indicators.

Process indicators are vital for the gathering of proof of the efficient completion of each stage of risk minimization measures. This group of process indicators shall facilitate the assessment of performance of the planned program and promote the required impact on behavior/actions of the target group. Program performance indicators shall be predetermined

and monitored during the entire effective period of the program. The acquired data and experience may be used for optimization of remedial actions (if necessary). Process performance evaluation will also improve understanding of the processes and causal mechanisms, facilitating (or hindering) the additional risk minimization measures succeed in gaining the desired control of specific risks.

The resulting indicators promote overall assessment of the risk control achieved through introduction of the risk minimization measures. For example, if the prompt measure aims to reduce the frequency and/or severity of the adverse reaction, the ultimate success criterion will be tied to this particular goal.

Conclusion about feasibility of further operation of the evaluated risk minimization measure without any changes or about the need for any changes in the conducted activities shall be based on the results of efficiency evaluation of the risk minimization measures. Efficiency evaluation of the risk minimization measures may indicate that the risk minimization activities are insufficient and need to be improved (e.g., by making amendments to the warnings or recommendations in the package insert or leaflet, or by giving clearer recommendations on risk minimization and/or by adding any new or improving the existing risk minimization tools). Efficiency evaluation may also find the risk minimization measures inadequate or lacking the proper focus, thereby causing reduction in the scope of operations under the program or streamlining the said program (e.g., by reducing the number of risk minimization tools/methods or decreasing the frequency of the measures implementation or number of elements repeated).

In addition to efficiency evaluation of the risk minimization in the context of safety concerns management, it is important to get an insight into whether the additional risk minimization measure is capable of causing any unintended (negative) consequences to the task of securing the public health in the short- or long-term.

#### *12.2.4.1. Process Indicators*

Process indicators include the parameters used in evaluation of performance of the original program and/or changes in its performance. Process indicators shall complement rather than replace evaluation of accomplishments by way of the risk minimization measures (i.e. result indicators). Depending on the nature of active measures, various process indicators may be identified for evaluation of their efficiency.

##### *12.2.4.1.1. Reaching the Target Population*

If the risk minimization measures envisage provision of information and guidelines to the healthcare professionals and/or patients by educational methods, data distribution should be evaluated so as to obtain basic performance data. These indicators shall focus on evaluation of the used tool for conformity with the target population (e.g., proper language, pictures,

diagrams or other graphics) or the actual distribution of the materials to the target group.

#### *12.2.4.1.2. Evaluation of Clinical Experience*

For the purpose of evaluation of awareness of the target population and the level of expertise reached by way of educational measures and/or provision of information (e.g., by way of package insert), analytical surveys should be conducted based on the strictly scientific methods.

The analytical survey usually implies standard questioning carried out by the phone or by personal interview or mailed/e-mailed by the interviewed and repeated from time to time. This kind of approach may be adapted to control of attitude and awareness in representative groups of healthcare professionals and/or patients with the help of the relevant psychometric values. The evaluation should be preceded by identification of the adequate scope of the random-based sampling.

Due attention should be given to the purpose of analytical survey, design of the trial, scope and representativeness of samples, prompt identification of dependent and independent variables, and to statistical analysis. Particular focus should be given to the choice of the most appropriate data collection tools (e.g., questionnaires, checklists, etc.).

#### *12.2.4.1.3. Evaluation of Clinical Actions*

Efficiency evaluation of the prompt educational measures and/or information support implies identification of clinical experience and the resulting clinical actions (e.g., prescription of the medicinal product). Research of medicinal product use by analysis of secondary data from digital medical records should be considered as valuable tool facilitating the quantification of clinical actions for each specific representative of the target group.

Analysis of the medicinal product administration records, especially in connection with other patient-related data (e.g., clinical, demographic, etc.), may facilitate evaluation of the medicinal products prescription, including prescription of two interacting medicinal products, promoting the compliance with laboratory monitoring, as well as selection of the patient and monitoring of its condition. Through application of statistical methods (e.g., analysis of statistical series, survival analyses, and logistic regression) to the medicinal products consumer cohort, various aspects of the medicinal products prescription or application can be evaluated, thereby promoting the understanding beyond the scope of exclusively descriptive evidence.

#### *12.2.4.2. Outcome Indicators*

Ultimate values indicative of successful risk minimization program are represented by the safety results, i.e. frequency and/or severity of the adverse reactions caused by the medicinal product taken by the patient outside of interventional study (i.e. within the scope of non-interventional studies). Safety data shall represent the outcome indicators.



Evaluation based on these indicators shall include matching of epidemiological frequency values, such as frequency rate or cumulative frequency of the adverse reaction obtained in the context of safety during the postmarketing phase. For any kind of approach, strict scientific and generally accepted principles of epidemiological trial shall always serve as the guide to evaluation of the ultimate results. Records of the frequency values should be kept before and after the risk minimization measures to facilitate comparison.

If the evaluation and calculations before and after the risk minimization measures is practically impossible (e.g., risk minimization measures put into effect at the time marketing authorization was granted), the outcome frequency value obtained after the completion of measures should be matched against the predetermined reference value obtained from scientific literature sources, retrospective data from the medical records of the patients, the expected frequency of occurrence within overall population (e.g., the *de facto* analysis as opposed to the expected one), and should consider the potential effect from encouragement of adverse event reporting. The choice of the comparison group shall be properly substantiated.

The level of spontaneous reporting (i.e. the number of suspected ICSRs over a fixed period of time) should not be treated as an acceptable evaluation of frequency of the adverse events within the population that is getting the treatment, excluding however special circumstances when the basic frequency of the adverse events within the group is negligible and there is a clear correlation between the treatment and the adverse reaction.

Under the circumstances when evaluation of the risk directly in the group concerned is practically impossible, spontaneous reports could be used as the basis for the assumption concerning the tentative value of frequency of the adverse reaction within the group, providing however that other reasonably substantiated data can be obtained for evaluation of the reporting level in the context of the medicinal product use. However, typical errors that affect the level of reporting of the suspected adverse reactions may yield misleading results. For example, introduction of the risk minimization program in response to a safety concern detected on the post-authorization stage of the medicinal product safety monitoring may promote the awareness of certain adverse reactions, ultimately resulting in higher reporting rates. In these circumstances, the analysis of spontaneous reporting may lead to a misleading conclusion that the intervention proved to be inefficient. Reduced values of reporting over a certain period may also result in misleading conclusions about the efficiency of intervention.

#### ***12.2.5. Coordination***

If several medicinal products containing the same active substance are available on the market, integral holistic approach should be worked out toward the additional measures that need to be taken with respect to risk minimization envisaged by the national competent

authorities of Member States. A coordinated approach shall be properly negotiated and when there is a need for coordinated activities with respect to the group of medicinal products. Under these circumstances, preliminary planning shall procure that the efficiency of risk minimization is evaluated for each individual product and for the group of medicinal products cumulatively.

#### ***12.2.6. Quality Risk Minimization System***

Even though the development and implementation of risk minimization arrangements may involve a number of various experts, the ultimate responsibility for quality, accuracy and scientific integrity of any such arrangements resides with the Marketing Authorization Holder and the authorized qualified person for pharmacovigilance of the relevant EAEU member.

The Marketing Authorization Holder shall be responsible for updating of the Risk Management Plan in response to any new piece of information, and shall apply the quality principles detailed in Section 2 herein. The traceable version controlled updates of the Risk Management Plan shall be submitted to competent authorities of Member States for consideration and evaluation. Any related safety reports, the Risk Management Plan and the risk management systems integrated therein, as well as any documents pertaining to the risk minimization measures, may be subject to the audit or inspection.

The Marketing Authorization Holder shall procure proper documentation of the mechanism of reporting of the trial results or evaluation of the efficient risk minimization measures. These documents may also be subject to the audit or inspection as the case may be.

### **12.3. Responsibility of the Competent authorities of Member States of the EAEU Members**

Competent authorities of Member States of the EAEU members shall be responsible for the performance of the additional risk minimization measures as condition to safe and efficient use of the medicinal product.

As regards the risk minimization measures enforced after the issue of the marketing authorization license, the national competent authorities of Member States should ensure prompt consideration of the submitted measures and coordination thereof with the Marketing Authorization Holder.

As and whenever necessary, the national competent authorities of Member States may provide assistance in coordination of the risk minimization measures introduced with respect to the generic medicinal products with the same active substance. If any additional risk minimization measures are required for the generic medicinal products due to the safety concerns about the active substance, these measures shall be brought in line with the risk minimization measures applicable to the reference medicinal product. Under certain

circumstances, hybrid medicinal products may necessitate the additional risk minimization measures that are normally applicable to the reference medicinal product (e.g., caused by different composition, prescription method or incompatibility issues).

Competent authorities of Member States shall procure the application of any risk minimization tool/method. Competent authorities of Member States and the Marketing Authorization Holder shall agree upon the format and means of the risk minimization tools/methods, including printed materials, Internet platforms and other audio and video equipment, as well as planning (schedule) of operational measures prior to the medicinal product marketing within their respective countries or as the case may be.

Competent authority of Member State should make an independent decision regarding the choice of the relevant national educational materials and/or other risk minimization tools/methods, and the competent authorities of Member States of the EAEU members shall agree upon the key elements of the Risk Management Plan. National competent authorities of Member States of the EAEU members shall monitor implementation of the risk minimization measures on the national level.

#### **12.4. Responsibility of the Marketing Authorization Holders**

The Marketing Authorization Holder shall clearly define the purpose of the suggested additional risk minimization measures and their efficiency indicators. Any additional operational risk minimization measures shall be developed in accordance with the general principles set forth in Section 12.2.1 and Section 12.2.2, and shall have properly documented proof in the risk minimization program (See Section 6).

Measures approved by the competent authority in the Risk Minimization Plan shall be taken on a national level. The Marketing Authorization Holder shall provide updates regarding the status of the additional risk minimization measures in accordance with terms and conditions agreed upon in advance with the national competent authorities of Member States, and notify the competent authorities of Member States on any changes, problems or issues arising in the course of performance of the additional risk minimization measures. Any changes concerning the tools/methods of the risk minimization measures shall be agreed with the national competent authorities of Member States prior to becoming effective.

In case of Internet tools/methods are used, the Marketing Authorization Holder shall comply with requirements applicable to each member of the EAEU with due consideration of accessibility, identifiability, responsibility, confidentiality and data protection requirements.

Marketing Authorization Holder of generic medicinal drug shall develop the risk minimization measures consistent with the scope, focus, contents and format of the

tools/methods applicable to the original medicinal product. Scheduling and planning of the operational measures shall be properly coordinated so as to minimize the load on healthcare system.

The Marketing Authorization Holder shall evaluate the efficiency of the risk minimization measures with respect to generic medicinal products in close cooperation with competent authorities of Member States. If the trials appear to be feasible, it is strongly recommended that the parties involved conduct joint trials so as to minimize the load on their respective healthcare systems. For example, if any prospective cohort study is assigned as necessary, the inclusion shall be independent from prescription of the medicinal product with a certain trade name or a certain manufacturer of the medicinal product. In these cases, registration of data pertaining to the certain medicinal product is vital for prompt identification of any new risk associated with any specific medicinal product.

The Marketing Authorization Holder shall control the results of the risk minimization measures included in the RMP. General principles of efficiency evaluation are set forth in Clause 12.2.4 of this Section.

The Marketing Authorization Holder shall report the results of efficiency evaluation of the additional risk minimization measures pertinent to evaluation of the risk-benefit balance in the Periodic Safety Update Report.

The Marketing Authorization Holder shall secure prompt communication with the competent authorities to facilitate the appropriate regulatory evaluation and actions.

### **12.5. Healthcare Professionals and Patients**

Cooperation between the healthcare professionals and the patients is an extremely important factor for the successful implementation of educational and/or controlled access programs for the purpose of optimization of the risk-benefit balance. The said parties are expected to pay due attention to any risk minimization measure that may be enforced with the purpose of promoting safe and efficient use of the medicinal products.

### **12.6 Impact of the Efficient Risk Minimization Measures on RMP and PSUR**

Updates of the periodic safety update report and the Risk Management Plan should include overall estimates of the additional risk minimization measures taken with the purpose of reducing the important safety risks in relation to use of the medicinal product. The RMP shall focus on how the current activity and its results affect the planning of the risk minimization measures and/or pharmacovigilance. The PSUR shall estimate the impact of the imposed measures on the safety profile and/or risk-benefit balance of the medicinal product. Focus

should be done on information gathered over the period of report or from the commencement of the latest risk minimization measures.

Results of the efficiency evaluation of the risk minimization measures in every case shall be included in the RMP. In the context of this critical evaluation, the Marketing Authorization Holder shall monitor the factors promoting the goals or, on the contrary, rendering the risk minimization measures inadequate/inefficient.

This kind of critical analysis may include reference to experience outside of the EAEU members (if any).

Efficiency evaluation of the risk minimization measures shall specifically focus on whether the said measures proved to be effective with respect to the target risk minimization. Evaluation should be performed based on combined values of the process and the results in accordance with Clause 12.2.4 herein. Risk minimization measures taken at the time of the issue of the marketing authorization and the measures made effective at a later date during the marketing phase should be clearly distinguished.

Efficiency evaluation of the risk minimization measures shall follow the recommendations below:

- the evaluation shall provide the context by way of
- a brief description of the enforced risk minimization measures and
- identification of their goals, and
- description of the chosen process and the result values.
- the evaluation shall contain the appropriate analysis of the nature of the adverse reactions, including their seriousness and preventability. Where appropriate, logistical factors should be included that are capable to affect the clinical performance of the risk minimization measures.
- the evaluation shall include the study of the risk minimization measures routinely performed in clinical practices, including every deviation from the original plan. This kind of evaluation may include the results of the medicinal product application studies.
- the result values (i.e., frequency and/or severity of the adverse reactions), as a rule, shall serve as the key milestones for the evaluation of whether the risk minimization measures have reached the goals.

Suggested changes with the purpose of improvement of the risk management measures shall be presented in the relevant section of the PSUR. The Risk Minimization Plan shall be updated with due regard for the incoming information about the efficiency of the risk minimization measures.

The RMP update frequency shall be proportionate to the risks caused by or resulting from the use of medicinal product. Each update of the RMP shall focus on the risk minimization program and on submission of updates for the risk minimization measures, where applicable. In case of partial updates, the sections affected by the update should be listed in the cover letter accompanying the submitted documentation. If the package insert needs to be changed based on the results of the risk minimization measures, the basis for and the required changes shall be substantiated by the PSUR submission that properly reflects the above mentioned aspects.

### **12.7. Transparency**

National competent authorities of Member States shall procure the transparency and accessibility of information on the risk minimization measures by placing the following data on the relevant Internet portals: the current version of package insert; summary of the Risk Management Plan, specifying the risk minimization measures taken.

## **13. ADDITIONAL MONITORING**

### **13.1. Introduction**

Pharmacovigilance is a vital function of the healthcare system, because it aims to promptly identify and respond to the potential safety concerns in related to the use of the medicinal products.

A medicinal product is authorised on the basis that, its benefit-risk balance is considered to be positive at that time for a specified target population within its approved indication. However, not all risks can be identified at the time of initial authorisation and some of the risks associated with the use of a medicinal product emerge or are further characterised in the post-authorisation phase of the product's lifecycle. A list of medicinal products that require the extended safety data collection after the authorization should be created as it secures the ability to conduct proper safety monitoring adequate to the level of risk associated with their use, which implies introduction of the concept of additional monitoring of certain medicinal products.

Competent authorities of Member States of the EAEU members shall make, keep updated and publish the index of the medicinal products (hereinafter – “the List”) that are subject to additional monitoring within the EAEU territory. The medicinal products included in the list should be marked in the package insert and the leaflet by the inverted black oblique triangle ▼ followed by the explanation: “This medicinal product is subject to additional monitoring. This will facilitate prompt detection of the new safety data. Healthcare professionals are kindly asked to report any suspected adverse reactions”.

### **13.2. Structures and Processes**

#### ***13.2.1. Principles of the Assignment of the Additional Monitoring Status to the medicinal Product.***

All medicines are authorised on the basis that the benefit of treatment is considered to outweigh the potential risks. To come to this conclusion for a marketing authorisation, data from clinical trials conducted during the development of a medicine are assessed. However, adverse reactions which occur rarely or after a long time may become apparent only once the product is used in a wider population and/or after long term use. In addition, the benefits and risks of a medicine may have been evaluated in conditions which may differ from those in everyday medical practice, e.g. clinical trials might exclude certain types of patients with multiple co-morbidities or concomitant medications. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. Marketing

authorisation holders and competent authorities continuously monitor medicinal products for any information that becomes available and assess whether it impacts on the benefit-risk profile of the medicinal product. However, for certain medicinal products enhanced post-authorisation data collection is needed to ensure that any new safety hazards are identified as promptly as possible and that appropriate action can be initiated immediately. Therefore, in order to strengthen the monitoring of certain medicinal products and in particular to encourage the spontaneous reporting of ADRs, the concept of additional monitoring has been introduced.

Additional monitoring status can be assigned to a medicinal product at the time of granting a marketing authorisation or in some cases at later stages of the product life cycle for a medicinal product for which a new safety concern has been identified. The additional monitoring status is particularly important when granting marketing authorisation for medicinal products containing a new active substance and for all biological medicinal products, which are priorities for pharmacovigilance.

Competent authorities may also require additional monitoring status for a medicinal product which is subject to specific obligations e.g. the conduct of a Post-Authorisation Safety Study (PASS) or restrictions with regards to the safe and effective use of the medicinal product.

#### 13.2.2. Data Exchange and Transparency

The additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions without creating undue alarm. This can be achieved for example by highlighting the need to better characterize the safety profile of a new medicinal product by identifying additional risks but placing those potential risks in the context of the known benefits for this product. A publicly available list of medicinal products with additional monitoring status should be kept up to date by the EAEU regulatory agency. In addition, healthcare professionals and patients should be enabled to easily identify those products through their product labelling. The publication of the list together with appropriate communication should encourage healthcare professionals and patients to report all suspected adverse drug reactions for all medicinal products subject to additional monitoring.

### **13.3. Criteria for including a medicinal product in the additional monitoring list**

#### ***13.3.1. Mandatory Inclusion Criteria***

List of the medicinal products that are subject to the additional monitoring shall include the following categories:



- medicinal products authorized within the EAEU member and containing a new active substance that is not authorized in any EAEU member as part of any other medicinal product at the moment of this regulation effective date ;
- biological medicinal products authorized within the EAEU member after the effective date hereof;
- medicinal products subject to the PASS by the request of the national competent authority of the EAEU member at authorization or after the date of the issue of the marketing authorization.

### ***13.3.2. Additional (Optional) Inclusion Criteria***

By request of the competent authority, medicinal products may be included at the list as the ones subject to the additional monitoring based on the following criteria:

- package insert of medicinal product contains conditions or restrictions with regard to the safe and effective use of the medicinal product;
- competent authority of EAEU member requires other measures to be taken for the promotion of the medicinal product safety under the risk management system;
- competent authority of the EAEU member obliges the Marketing Authorization Holder to conduct the post-authorization efficacy study.

Decision on inclusion of medicinal product as the one to additional monitoring list shall also consider feasibility of this status taking into account any other additional pharmacovigilance measures suggested by the Risk Management Plan.

## **13.4. Criteria of Determining the Zero Point for Revision of the List of Medicinal Products Subject to Additional Monitoring**

### ***13.4.1. Mandatory Criteria***

For medicinal products containing new active substances and for all biological medicinal products, the initial inclusion period shall be 5 (Five) years from the date of the marketing authorization within the EAEU member.

### ***13.4.2. Additional Criteria***

For medicinal products included in the list based on certain established terms and conditions (performance of Post-Authorization Safety Studies, efficiency studies, requirements to risk management), is subject to compliance with certain terms, conditions and obligations of the Marketing Authorization Holder, and shall be determined by the national body of EAEU member state competent authority based on proper performance and the results thereof.

During the life cycle of medicinal product, the medicinal product can be included to the

list of additional monitoring several times.

### **13.5. Duties of the competent authorities of Member States members of EAEU**

National competent authorities of Member States should:

- a) notify the competent authorities of Member States of the other EAEU member states on the decision to include the authorized medicinal products in the list of medicinal products subject to additional monitoring; give the link to the national Website of the competent authority that provides open access to information about the medicinal product and to the summary of the Risk Management Plan;
- b) publish on the national Websites the list of medicinal products authorized within the relevant territories and subject to additional monitoring. The list should give the link to the Website of the competent authority that provides open access to information about the medicinal product and to the summary of the Risk Management Plan;
- c) inform the competent authorities of Member States of the other EAEU members about national authorization of the medicinal products that are listed as subject to additional monitoring;
- d) determine the frequency and specific signal detection procedures based on the list of medicinal products subject to additional monitoring;
- e) notify the relevant Marketing Authorization Holder on the decision to include its medicinal product to the list of subjects to additional monitoring;
- f) take all appropriate measures, to make sure that the healthcare professionals and patients report any suspected adverse reactions to the medicinal product listed as subject to additional monitoring; and
- g) update the additional monitoring medicinal products list on a monthly basis.

### **13.6. Duties of the Marketing Authorization Holders**

The Marketing Authorization Holder shall:

- - add to the package insert and leaflet of its medicinal products listed as subject to additional monitoring the symbol of the black triangle ▼ and a standard explanation disclaimer about the additional monitoring;
- include information about the additional monitoring status in every material that is to be distributed among the healthcare professionals and patients, and endeavor its best effort to encourage the reporting of adverse reactions in accordance with agreement with the national competent authorities of Member States;

- submit to the competent authorities of Member States all the appropriate data and proof of compliance with any specific conditions set by the national competent authorities of Member States; and
- acting in accordance with applicable laws of Eurasian union approved by Eurasian commission, submit relevant changes to the package insert and the leaflet regarding the inclusion/removal of the black symbol and the standard explanatory note.

### **13.7. Black Symbol and Explanatory Note**

For medicinal products listed as those subject to additional monitoring, the package insert and the leaflet shall contain the symbol of inverted black triangle ▼ followed by:

“This medicinal product is subject to additional monitoring. This will facilitate prompt detection of the new safety data. Healthcare professionals are kindly asked to report any suspected adverse reactions.”

After the medicinal product has been added to or removed from the list, the Marketing Authorization Holder shall make the appropriate modification to the package insert and the leaflet so as to add/remove the black symbol, statement and the standard explanatory note. If decision on the inclusion/removal of the medicinal product to/from the list is made in the course of the regulatory procedure (e.g., authorization/extension, changes in or to the package insert, etc.), the package insert and the leaflet need to be updated prior to the completion of the procedure in order to add/remove the black symbol and the explanatory note as the case may be. If the decision to add/remove the medicinal product to/from the list is made beyond the scope of the regulatory procedure, the Marketing Authorization Holder shall modify the package insert and the leaflet accordingly and pursuant to procedures envisaged by applicable laws.