ANNEX

to Decision No. 81
of the Eurasian Economic Commission's
Council dated May 19, 2022

AMENDMENTS
to the Rules of Good Pharmacovigilance Practice of the Eurasian Economic Union

The Rules shall read as follows:

APPROVED

by Decision No. 87 of the Eurasian
Economic Commission's Council dated
November 3, 2016
(as amended by Decision No. 81 of the
Eurasian Economic Commission's
Council dated May 19, 2022)

RULES
of Good Pharmacovigilance Practice of the Eurasian Economic Union

I. General Provisions

1. These Rules are developed in accordance with Article 12 of the Agreement on Common Principles and Rules for the Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014, to determine the procedure for exercising pharmacovigilance in the Member States of the Eurasian Economic Union (hereinafter, respectively, the Member States, the Union).

The objectives of pharmacovigilance are as follows:

Prevention of unfavorable consequences of adverse reactions in humans, developing after the use of authorised medicinal products following or not following the terms of the marketing authorisation or as a result of exposure related to professional activities.

ensuring the safe and effective use of medicines, particularly by providing timely information on the safety of medicines to patients, healthcare professionals, and the public.

2. For the purposes hereof, the concepts having the following meanings shall be used:

“Audit” is a systematic, orderly, independent, and documented process of obtaining and objectively assessing audit facts characterizing the operation of the pharmacovigilance system to determine the degree of fulfillment of the audit criteria;

“Important identified risk” and “important potential risk” are the identified risks or potential risks of the medicinal product use that may have an impact on the risk-benefit ratio or have consequences for public health. Determining a risk as important depends on several factors, including the degree of influence on the individual, the risk severity, and the impact on public health (health of population). Unless a marketing authorisation holder has justified otherwise, any risk that presumably should be included in the Contraindications and Precautions section pertains to important risks;

“Signal validation” is the process of evaluating the data on an identified signal to verify and confirm that the available information contains sufficient evidence to support the identification of a new potential causal link or a new aspect of a known association and therefore justifies the need for a set of further actions to analyze the signal;

“Validated signal” is a signal for which, in the course of validation and evaluation of supporting data, it has been established that the available documentation is sufficient to suggest the presence of a new potential causal link or a new aspect of a known association between the intake of a suspected medicinal product and the development of an adverse effect and, accordingly, the need for a complex of further actions to evaluate the signal;

“Occupational exposure” is the impact of a medicinal product to which a person has undergone as a result of performing both professional and non-professional activities. Such exposure does not include the cases of exposure of one of medicinal product ingredients at the production stage before its release as a finished medicinal product;

“Signal detection” is the process of searching and/or identifying a signal using all safety data sources;

“Data lock point” is a date of completion of data collection for inclusion in the periodic safety update report; based on the international birth date. Within the development safety update report, it is a date of completion of data collection for inclusion in the report, based on the development international birth date. Data lock point includes the day and month;

“Completed clinical trial” is a trial for which the final study report was prepared.

“Closed signal” is a signal whose assessment has been completed during the reporting period of compiling a periodic safety update report;

“Abuse of medicinal products” is a persistent or one-time voluntary overuse of a medicinal product, accompanied by adverse physiological or psychological effects;

“Identified risk” is an adverse pharmacotherapeutic outcome for which there is sufficient evidence of a relationship with the suspected medicinal product;

“Individual case safety report (ICSR)” (adverse (drug) reaction report) is the information transmitted in accordance with the established form and content about one or more suspected adverse drug reactions that occurs in an individual patient at a certain point in time;

“Medicinal product incident” (incident) is a situation in which an event occurs, or new information is received regarding an authorised medicinal product, whether or not it is available, which may have a severe impact on public health (health of population);

“Solicited sources of individual case safety reports” are organised data collection systems that include clinical trials (studies), registries, post-authorisation personalised medicine use programs, other programs for patient support, disease monitoring, interviewing patients or attending physicians, or collecting information about the treatment efficacy and patients’ compliance;

“Quality of a pharmacovigilance system” is all pharmacovigilance system characteristics that, according to the likelihood assessment, lead to results consistent with the proper pharmacovigilance system’s objectives;

“Clinical trial (study)” is a clinical study of a medicinal product that satisfies at least one of the following conditions:

The study subject distribution to a specific therapeutic strategy (intervention) occurs in advance, and it is not a routine clinical practice (that is, standard (uniform) medical diagnostic and therapeutic procedures, technologies, or activities that are performed for a given group of patients or a given standard of care) in a Member State, where study sites are involved in this clinical study;

the decision to prescribe the study product is made in conjunction with the decision to include a subject in the clinical trial;

study subjects, in addition to the routine clinical practice procedures, undergo additional diagnostic or monitoring procedures;

“Quality control and assurance” include monitoring, assessment, ensuring the efficacy and accordance of the structural elements and processes of the pharmacovigilance system with the established requirements;

“Drug (medicinal product)” is an agent representing or containing a substance or a combination of substances intended for the treatment, preventive treatment of human diseases, or restoration, correction, change of physiological functions through pharmacological, immunological, or metabolic effects, or diagnosis of diseases and human conditions;

“Medicinal product” is a drug (remedy) in a dosage form that comes into contact with the human body;

“Pharmacovigilance System Master File (PSMF)” is a detailed description of the pharmacovigilance system used by a marketing authorisation holder concerning data on one or more authorised medicinal products;

“Development International Birth Date (DIBD)” is the date of the first approval (authorisation) of the interventional clinical trial in any country of the world;

“International Birth Date (IBD)” is the date of the first registration (approval for use) of a medicinal product containing a specific active ingredient in any state;

“Risk minimisation measures (activity)” is a set of measures to prevent or reduce the likelihood of adverse reactions associated with medicinal product exposure or to reduce the severity or impact of adverse reactions on the patient in the event of their development;

“Minimum criteria for reporting about an adverse reaction” are the minimum data submitted to the authorised pharmacovigilance authority on cases of detecting some suspected adverse reactions (including an identifiable

reporter, an identifiable patient, an adverse reaction and a suspected medicinal product);

“Set of data for analysis” is the minimum set of data required to perform the statistical analysis required to obtain results for the study’s primary objectives;

“Good Pharmacovigilance Practices” (GVP) is the guidance pharmacovigilance implementation in the Member States of the Eurasian Economic Union, the requirements of which apply to marketing authorisation holders and authorised authorities of the Member States;

“Study start date” is the date of the start of data collection;

“Start of data collection” is the date of registering the data on the first patient included in the study in documentary form (electronic data collection database) or the date of the start of data retrieval (in case of data reuse);

“Non-validated signal” is a signal for which, based on the results of validation and evaluation of the supporting data, it is determined that the available data are insufficient to suggest the presence of a new potential causal link or a new aspect of a known association and, accordingly, further signal analysis is not reasonable;

“Adverse reaction” is an unintentional unfavorable reaction of the body associated with using a medicinal product and suggesting a relationship with the use of a suspected product. In the case of a spontaneous report of adverse event development, in which the causal link is unknown or not indicated by the healthcare professional or the original consumer, this adverse event is considered an adverse reaction. All incoming spontaneous reports presented by healthcare professionals or consumers are considered suspected adverse reactions because their presentation contains a reporter’s assumption that there is a relationship. The exception is reports in which the primary source indicates the absence of a relationship between the adverse event and the

suspected medicinal product's intake. Adverse reactions can occur when the medicinal product is used according to or in violation of the approved conditions for the use of the product or as a result of occupational exposure. Cases of violation of the approved conditions of the medicinal product use include not following the summary of product characteristics or the package inserts regarding the use of the product, overdose, abuse, misuse and medication errors;

"Adverse event" is any unfavorable change in the state of health of a patient or study subject that occurred after the medicinal product use, regardless of the causal link with its use. An adverse event can be any unfavorable and unintentional change (including abnormal laboratory findings), a symptom or disease, the time of occurrence of which does not exclude a link with the drug use, regardless of the presence or absence of a relationship with the product used;

"Adverse event following immunisation" is any adverse event that develops after immunisation, regardless of the presence or absence of a relationship with the use of the vaccine. An adverse event following immunisation can be any adverse and unintended change (including abnormal laboratory findings), symptom or disease;

"Non-interventional study" is a study that meets the following conditions:

a medicinal product is prescribed following the summary of product characteristics;

the decision to prescribe a particular treatment to the patient is not made in advance according to the study protocol but in accordance with a routine clinical practice, and the prescription of the medicinal product is separated from the decision to enroll the patient in the study;

as regards patients undergo no additional diagnostic or control procedures, and epidemiological methods are used to analyze the data obtained;

“Misuse” is an intentional and inappropriate use of a medicinal product that does not comply with the conditions established during the marketing authorisation of the medicinal product;

“Misuse of a medicinal product for illegal purposes” is misuse with the additional hidden intent of misusing a medicinal product to influence another person. Misuse for illegal purposes includes the sale of medicinal products to another person for recreation and the use of products to commit criminal acts;

“Unexpected adverse reaction” is an adverse reaction, the nature, severity, or outcome of which does not correspond to the information contained in the current summary of medicinal product characteristics. Unexpected adverse reactions include pharmacological class effects indicated in the summary of product characteristics that have not been described as drug-related directly. For medicinal products authorised in accordance with a Member State’s legislation, the summary of product characteristics is applied, approved by the Member State’s authorised pharmacovigilance authority that received the adverse reaction report;

“Newly identified signal” is a signal first identified during the reporting period of the periodic safety update report, which is the basis for further action or its assessment.

“Data lock point” is a date when the data collection base is for the first time fully available and suitable for analysis;

“Organisation” is a legal entity authorised to carry out pharmacovigilance activities and responsible for implementing this activity;

“Company core safety information (CCSI)” is information related to the safety of a medicinal product contained in the list of the marketing

authorisation holder's primary product data, developed by the holder and submitted, upon his/her request, to the authorised pharmacovigilance authorities of the Member States of the Eurasian Economic Union, where this medicinal product is marketed, except for the cases when changes are made to the information at the request of these authorised pharmacovigilance authorities. The marketing authorisation holder's core safety information is reference data that determine the status of listed and unlisted adverse reactions to compile a periodic safety update report on a medicinal product but do not define expected and unexpected adverse reactions to meet the requirements for immediate reporting of adverse reactions;

"Company core data sheet" is a document developed by a marketing authorisation holder, containing safety information, indications, dosage regimen, pharmacological properties, and other product-related information;

"Refuted signal" is a validated signal, which, according to the subsequent assessment results, was determined as false due to the impossibility of confirming the presence of a causal link for the current period of time;

"Missing information" is a lack of safety information or on the product administration details in certain patient groups that may be clinically significant;

"Development safety update report (DSUR)" is a periodic safety update report for a developed medicinal product;

"Signal assessment" is a process for further evaluating a validated signal using all available data to examine evidence of a causal link between a new risk and an active drug substance or to determine a change in the known risk characteristics;

"Medication error" is an unintentional error in the process of using a product that has led or could harm a patient;

“Overdose” is a single-dose or multiple-dose drug administration in amounts that exceed the recommended maximum dose following the current summary of product characteristics;

“Periodic safety update report (PSUR)” is a report for presenting an assessment of the risk-benefit ratio of a medicinal product by a marketing authorisation holder in a certain period of time during the post-authorisation period;

“Audit plan” is a description of the planned activities and the arrangement of a separate audit;

“Risk management plan” is a detailed description of the risk management system;

“Quality planning” is creation of the quality system structure of the pharmacovigilance system and planning of integrated and coordinated processes of the pharmacovigilance system’s quality system;

“Post-authorisation safety study (PASS)” is a study related to an authorised medicinal product carried out to define, characterize, or quantify a safety threat, confirm the safety profile of a medicinal product, or evaluate the effectiveness of risk management measures. A post-authorisation safety study is organised as an interventional clinical trial or conducted as an observational non-interventional design study, including with the use of real-world data;

“Potential risk” is an undesirable consequence of pharmacotherapy, in respect of which there are grounds for suspicion of a relationship with the medicinal product, which has not been properly confirmed.

“Consumer” (consumer)is a patient, a caregiver, interacting with them but not being a healthcare professional;

“Quality adherence” is the fulfillment of tasks and responsibilities in accordance with quality requirements;

“Off-label use is an intentional use of a medicinal product for a medical purpose, not following the summary of product characteristics or patient information leaflet;

“Compassionate use of a medicinal product” is a compassionate prescription of a medicinal product to a group of patients with chronic, disabling, or life-threatening illnesses and diseases that cannot be cured using authorised medicinal products (the corresponding product must be at the stage of authorisation or clinical trials);

“Signal prioritisation” is a continuous process throughout all stages of management, the signal and purpose of which is to identify signals of perceived risks with a significant potential impact on the patient or public health (health of population) or signals that can have a considerable effect on the risk-benefit ratio of a medicinal product, and, accordingly, immediately require response and risk management actions;

“Safety concern” is an important identified risk, important potential risk, or missing information;

“Audit program” is a sequence of one or more audits planned for a specified period of time and with a specific purpose;

“Ongoing clinical trial” is the trial in which the inclusion of patients began, even if the trial is suspended or its analysis is completed, but there is no final report on it;

“Direct healthcare professional communication” is a communication tool with the help of which important information is provided directly to certain healthcare professionals designated by a marketing authorisation holder or authorised pharmacovigilance authority to inform them of the need to take specific measures or change their routine practice in connection with important new drug data received;

“Ongoing signal” is a signal undergoing the evaluation procedure as of the end date of collecting the periodic safety update report data;

“Immunisation anxiety-related reaction” is an adverse event after immunisation that develops due to anxiety about immunisation;

“Registry” is an organised system that uses observation methods to collect standardised data on analysed outcomes in a population of patients with certain diseases, conditions or patients exposed to certain influences;

“Audit findings” are results of a conformity assessment of the facts obtained from the audit results with the audit criteria;

“Audit recommendation” is a description of the course of action that the management is entitled to take for correcting the deficiencies and inconsistencies identified after the audit and minimizing the weaknesses in the management control systems;

“Reporting” the process of transmitting, in the established form, information about adverse reactions to the authorised pharmacovigilance authorities or expert organisations whose competence includes pharmacovigilance;

“Risks associated with the use of a medicinal product” are risks associated with the quality, safety, or efficacy of the medicinal product concerning the patient or public health or leading to a negative impact on the environment;

“Serious adverse reaction” is an adverse reaction that leads to death, poses a threat to the patient’s life, requires hospitalisation of the patient or prolonged hospitalisation, leads to a persistent or severe loss of ability to work or disability, to congenital anomalies or developmental defects; Any unintentional suspected transmission of an infectious agent through a medicinal product is also considered a serious adverse reaction;

A life-threatening condition in this context means a reaction in which the patient’s life was threatened at the time the reaction developed. This condition does not refer to a reaction that could hypothetically lead to death in the event of a more severe disease progression.

The decision to classify situations as serious adverse reactions, such as medically significant events that do not pose an immediate threat to the patient’s life, do not result in death or hospitalisation but put the patient at risk or require intervention to prevent one of the outcomes listed in the said definition is taken based on medical and scientific judgment, including for conditions requiring intensive care in the emergency department or at home in case of allergic bronchospasm or seizures that do not require hospitalisation and in case of developing the dependence or abuse of the medicinal product, which should also be considered serious adverse events;

“Signal” is information coming from one or more sources, including observations and experiments, which suggests the presence of a new potential causal link or a new aspect of a known association between the drug effect and an event or a set of interrelated events, adverse or beneficial, assessed as sufficient for further action for signal verification. New aspects of a known association may include changes in frequency, distribution of adverse reaction (e. g., by sex, age, and territory), duration, severity, or outcome of the adverse reaction;

“Quality system of a pharmacovigilance system” is the organisational structure, responsibilities, procedures, processes, and resources of the pharmacovigilance system, including the proper management of resources, documentation, and regulatory compliance;

“Risk management system” is a set of actions and measures for pharmacovigilance to identify, characterize, prevent, or minimize the drug-

related risks, including assessing the effectiveness of these measures and activities;

“Pharmacovigilance system” is a system organised by marketing authorisation holders and authorised pharmacovigilance authorities to fulfill the tasks and pharmacovigilance responsibilities designed to control the safety of medicinal products, timely detection of all changes in the assessment of the risk-benefit ratio of medicinal products for developing and implementing the measures to ensure the use of medicinal products when a benefit exceeds a risk;

“Healthcare professionals” are persons with medical qualifications (for example, doctors, pharmacists, pharmacists, nurses and forensic experts). This definition is used, among other things, in the context of reporting suspected adverse reactions;

“Spontaneous report (notification)” is a voluntary transfer by a healthcare professional or consumer to an authorised pharmacovigilance authority, a marketing authorisation holder, or another authorised organisation (including the World Health Organisation, regional pharmacovigilance centers, toxicological centers) of data that contain a description of one or more adverse reactions in a patient taking one or more medications that were not obtained in the course of a clinical trial or using another method of organised data collection;

“Reference safety information” is information on the safety of the medicinal product included in the core information on the medicinal product of a marketing authorisation holder (e. g., the core data sheet of the marketing authorisation holder), and which the marketing authorisation holder must indicate in all periodic safety update reports in all states where the medicinal product is sold, for except for cases when a authorised pharmacovigilance authority requires changes to the reference information;

“Significant changes in the study protocol” are changes in the study protocol that may affect the safety, physical or mental well-being of study subjects, or affect the interpretation of study results (e. g., changes in the primary and secondary objectives of the study, the study population, sample size, study design, the source of the data obtained, the method of data collection, the determination of the main exposure, the outcomes and combination variables in the statistical data analysis plan);

“Quality requirements” are characteristics of the quality system that, with a certain probability, lead to the achievement of the quality system’s required results or objectives;

“Quality improvement” is making the necessary changes to structure and processes of the pharmacovigilance quality system to improve the quality assurance system;

“Signal management” is a set of measures taken to determine the presence of new risks associated with an active ingredient or medicinal product, or to change known risks based on the results of analyses of individual case safety reports (ICSRs), aggregate data obtained from existing active monitoring systems, or studies, scientific literature or other data sources, and to adopt some necessary recommendations, solutions, information exchange, and tracking.

Pharmacovigilance is a scientific and practical activity to identify, assess, understand, and prevent undesirable consequences of drug administration. Therefore, pharmacovigilance is an activity directed to protecting patient and public health;

“Target population (treatment) (treatment population target)” are patients to whom a medicinal product is prescribed following the indications and contraindications provided for by the current summary of product characteristics;

“Emerging safety issue” is a safety-related issue assessed by a marketing authorisation holder as requiring urgent attention of the authorised pharmacovigilance authority due to the significant potential impact on the risk-benefit ratio of the medicinal product and/or on the patient or public health (health of population) and due to the potential need for immediate taking regulatory action and informing patients and healthcare professionals.

The “risk-benefit ratio” concept used in these Rules is used in the meaning determined by the Rules for Marketing Authorisation and Expert Assessment of Medicinal Products for Human Use, approved by Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016 (hereinafter referred to as the Rules for Marketing Authorisation and Expert Assessment).

II. Requirements for the Quality System

1. Quality System

3. The quality system is an integral part of the pharmacovigilance system. Concerning good pharmacovigilance practice, which defines the requirements for a pharmacovigilance system’s structure and processes, a quality is a set of characteristics of a pharmacovigilance system that allows, according to the assumed probability, to achieve system performance results consistent with the objectives of pharmacovigilance. The need to assess the degree of achievement of the required level of system quality determines the need for predefined quality requirements. Quality requirements are defined characteristics of the system, the fulfillment of which, with a certain probability, allows achieving the planned results, i. e. objectives of the quality system. The general objectives of the quality system in the pharmacovigilance system are defined in paragraph 6 of these Rules. Specific

objectives and quality requirements for individual structures and processes of the pharmacovigilance system are set forth in Sections IV - VII and IX - XIII of these Rules.

4. The quality system shall cover the organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system. The quality system shall include:

proper resource management;

control of compliance with the requirements of the Union authorities' acts and the Member States' legislation;

and document management.

5. The quality system provides for the cyclical implementation of the following activities:

a) planning the quality of pharmacovigilance works;

b) fulfilling tasks and responsibilities pursuant to the quality requirements (quality adherence);

c) monitoring and evaluating the effectiveness of the organisation and operation of the pharmacovigilance system's structures and processes (quality control and assurance);

d) adjusting and improving the structure and processes of the pharmacovigilance system (quality improvement).

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

a) fulfilling the requirements and obligations for pharmacovigilance in accordance with the Union authorities' acts and the Member State's legislation;

b) preventing any undesirable consequences of the use of authorised medicinal products;

c) ensuring the use of products when a benefit exceeds a risk;

d) promoting patient and public health (health of population) protection.

2. Good Pharmacovigilance Practice Principles

7. To fulfill the objectives specified in paragraph 6 of these Rules, the following principles should be adhered to when developing structures and processes of pharmacovigilance system, as well as in performing all tasks and responsibilities:

a) ensuring that the needs of patients, healthcare professionals, and public requirements are met concerning the safety of medicinal products;

b) providing effective guidance on the implementation of the quality system and personnel motivation in relation to the objectives of the quality system;

c) involvement of all employees of the organisation (enterprise) in the process of supporting the pharmacovigilance system at the level of their assigned responsibilities;

d) involving all employees of the organisation (enterprise) in the continuous process of improving the pharmacovigilance system quality in accordance with the cycle of activities specified in paragraph 5 of these Rules;

e) organizing the resource base and solving the tasks assigned to the pharmacovigilance system in the form of structures and processes in such a way as to ensure active, consistent with the risk level, continuous pharmacovigilance activities;

f) taking into account and evaluating any available evidence on the risk–benefit ratio. To make further decisions, all data that may have an impact on this ratio and the use of the medicinal product shall be considered and evaluated.

g) promoting the development of effective cooperation between developers, marketing authorisation holders, authorised pharmacovigilance authorities (hereinafter referred to as the authorised authorities), healthcare institutions, patients, healthcare professionals, scientific organisations, and other persons concerned in accordance with the Member States' legislation.

3. Parties Responsible for the Quality System

8. All specialists involved in organizing the quality system are responsible for ensuring that the pharmacovigilance system operates in accordance with the quality system requirements. The organisation shall provide a sufficient number of authorised and trained professionals with appropriate training to carry out the required amount of pharmacovigilance activities at an appropriate level. Their duties shall include compliance with the measures set out in paragraph 5 of these Rules.

9. A systematic approach to quality assurance in the pharmacovigilance system shall be ensured by the managers of the organisation. As part of their systems approach functions, managers of organisations are responsible for ensuring:

a) the quality system documentation in accordance with the requirements of Subsections 9–11 of this section;

b) proper control and documentation of all changes in the pharmacovigilance system and the pharmacovigilance quality system;

c) resources required for proper training;

d) required resources (including the necessary premises and equipment, etc.);

e) good compliance management;

f) proper records management;

g) performing regular assessments of the pharmacovigilance system activities, including the integrated quality system and confirmation of its effectiveness. If necessary, corrective and preventive actions shall be implemented.

h) existence of an effective mechanism for implementing appropriate actions in the event of changes in the safety profile of developed and manufactured medicinal products;

i) timely identification and adoption, if necessary, of corrective and preventive actions in case of non-compliance with the pharmacovigilance system quality requirements;

j) conducting regular audits of the system.

4. Personnel Training

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

11. The organisation shall establish and implement a training plan for pharmacovigilance specialists and shall maintain records to document training and maintenance and development of personnel competence. The training plan should be based on an assessment of the need for training. The development and implementation of the plan are subject to control and monitoring.

12. Training shall include introductory training and subsequent training throughout the work period in accordance with the functions performed and the tasks assigned. Training shall be aimed at improving the relevant professional skills, introducing scientific advances into practice and the procedures performed, ensuring that all specialists meet the requirements for

qualifications, professional skills, knowledge and understanding of the performed procedures related to pharmacovigilance. All employees shall be trained to perform the procedures for receiving information on a safety concern about medicinal products.

13. The organisation's training processes shall include monitoring the training results to achieve the required understanding and performance of pharmacovigilance functions and determine the need for further training following the organisation's and specialists' professional development plans.

14. The organisation requires appropriate training in certain aspects of pharmacovigilance for specialists from other departments, whose activities can affect the pharmacovigilance system's performance and the performance of pharmacovigilance functions. These activities include, among other things, conducting clinical trials, handling claims, preparing medical information, selling and marketing, preparing authorisation documents, legal issues, and auditing.

5. Pharmacovigilance Tools and Equipment

15. Achieving the required level of quality in implementing pharmacovigilance processes and the obtained results is also associated with providing the system with the necessary tools and equipment used in these processes.

16. Tools and equipment shall be located, designed, adapted, and maintained in such a way as to meet the stated purpose following the quality objectives of pharmacovigilance. Tools, equipment, and their functional properties, important for pharmacovigilance, are subject to appropriate testing, qualification, and/or validation to confirm their compliance with the purpose. A documented risk assessment should be used to determine the scope of testing, qualification, or validation. This risk management method

should be applied throughout the life of the tools and equipment, taking into account factors such as the influence on patient safety and data quality and the complexity of tools and equipment involved. The organisation of the functioning of information systems shall provide processes for ensuring the compliance of the used terminology with the current updated versions of the used international terminology to introduce timely changes in the information systems used.

6. Ensuring the Compliance with Requirements of the Union Authorities' Acts and the Member States' Legislation by Marketing Authorisation Holders

17. To ensure compliance with Union authorities' acts and the Member States' legislation, the holders of marketing authorisation for medicinal products shall carry out the system quality assurance processes, which objectives include:

a) continuous monitoring of pharmacovigilance data, development and implementation of risk minimisation measures when determining their need, proper assessment of safety data regardless of the source of their receipt (from patients, medical and pharmaceutical workers published in the scientific medical literature, identified during post-authorisation studies);

b) scientific evaluation of all the medicinal product's safety information, including information on adverse reactions that have developed, including when used following or not following the approved summary of product characteristics or instruction for medical use (package insert) (hereinafter referred to as the patient information leaflet);

c) compliance with the requirements of the Union authorities' acts and the Member State's legislation to provide the authorised authority with complete, accurate and reliable information on adverse reactions and other

information on the medicinal product safety in accordance with the reporting periods established by the Member State’s legislation;

d) ensuring the quality, integrity, and completeness of the information provided on the risks of medicinal products, including processes for eliminating duplicate information and proper validation of signals;

e) ensuring effective communication with the authorised authorities, including informing about changes in the safety profile of medicinal products and new risks, the pharmacovigilance system master file, risk management system, risk minimisation measures, periodic safety update reports, corrective and preventive actions, post-authorisation safety studies;

f) ensuring the compliance of the information on medicinal products (summary of product characteristics, patient information leaflet) with the state-of-the-art level;

g) providing healthcare professionals and patients with safety information.

7. Ensuring Compliance with the Requirements of the Union Authorities’ Acts and the Member States’ Legislation by the Authorised Authorities

18. Authorised authorities shall have an appropriate process quality assurance system in place for the purposes of:

a) assessing the quality of submitted pharmacovigilance data;

b) assessing and processing the pharmacovigilance data in accordance with the requirements of the Union authorities’ acts and the Member States’ legislation;

c) ensuring guaranteed independence in the performance of pharmacovigilance activities;

d) effective information exchange with patients, medical workers, marketing authorisation holders and society as a whole;

e) carrying out inspections, including a pre-authorisation inspection.

19. Independence in the performance of pharmacovigilance activities is determined by adopting all regulatory decisions only in the interests of the patient and public health (health of population).

8. Document Management

20. The document management system is part of the quality system, applies to all documents of the pharmacovigilance system, and provides the ability to search for data and traceability of the procedures performed, including procedures for evaluating new data and investigating the safety concerns in respect to the processes correctness, the time of investigation and decision making.

21. The document management system shall ensure the following:

a) quality management of pharmacovigilance data, including their completeness, accuracy, and integrity;

b) timely access to all records;

c) effective internal and external data transfer;

d) storage of documents related to pharmacovigilance systems and implementing pharmacovigilance for each of medicinal products according to applicable shelf life.

22. A holder of a marketing authorisation for a medicinal product (hereinafter referred to as the MA holder) shall ensure proper documentation, circulation, and storage of all pharmacovigilance information to carry out procedures for accurate reporting, interpretation, and verification of data. A MA holder must provide a system for the traceability and subsequent monitoring of adverse reaction.

23. The document management system shall include a set of measures to ensure data security and confidentiality to fulfill the requirements for the

protection of patients' personal data in accordance with the requirements of the legislation of the Member State. The document management system shall provide special measures at each stage of storage, processing, and transmission of pharmacovigilance data while ensuring data security and confidentiality. These measures shall include a strict data access restriction, according to which access to documentation and databases shall be limited by authorised persons.

24. The document management system shall include processes to ensure the protection of pharmacovigilance information from loss and destruction.

25. The document control system shall be described in the document management policy.

9. Quality System Documentation

26. All elements, requirements and provisions of the quality system shall be properly documented and systematised in the form of a quality plan, quality manual, quality procedures and quality reports.

27. The quality plan defines the quality system's main objectives and the processes that must be implemented to achieve the stated objectives. Quality procedures describe an established order of execution of processes and may be standard operating procedures and work instructions or manuals. The quality manual defines the scope of the quality system, the quality system processes, and their relationship. Quality reports include the results obtained from the system or the confirmation of the activities performed.

28. To ensure a systematic approach to quality planning, the organisation shall determine:

Quality objectives in accordance with the general objectives of the pharmacovigilance quality system in accordance with paragraph 6 of these

Rules and quality objectives specific for individual structures and processes in accordance with the relevant sections of these Rules;

b) methods of monitoring the pharmacovigilance system effectiveness.

29. The quality system existence and operation are documented by using:

a) organisational structure and personnel responsibilities documentation;

b) training plans and training records;

c) instructions for management processes implementation in accordance with the Member State's legislation;

d) instructions on the processes to be followed in a situation requiring urgent actions, including business continuity procedures;

e) process performance indicators used to continuously monitor the proper performance of pharmacovigilance functions;

f) reports on the audit and subsequent audit of the quality system, including the findings and results.

30. The quality system documentation shall also include:

a) methods for monitoring the quality system effectiveness and, in particular, its ability to achieve the quality system objectives;

b) records management policy;

c) documents on the results of the performed pharmacovigilance procedures, confirming the performance of the specified stages and actions;

d) documents and reports on tools and equipment, including verification of functional properties, qualification and validation activities, which confirm the completion of all stages stipulated by the relevant requirements, protocols, and procedures;

e) reports confirming the control of deficiencies and deviations from the established quality system, taking preventive and corrective measures, and evaluating the measures taken.

10. Additional Documentation on the MA Holder's Quality System

31. In addition to the required quality system documentation, a MA holder must document:

a) human resource management;

b) duties and functions of the pharmacovigilance system personnel;

c) an organisational structure that defines the hierarchical relationship of management and supervisory personnel and a resource management system;

d) instructions for performing critical processes;

e) document management system.

11. Additional Quality System Documentation of Authorised Authorities

32. In addition to the required quality system documentation, the authorised authority shall document the organisational structure, distribution of tasks and responsibilities between all personnel of the pharmacovigilance system, and appoint contact persons to ensure interaction between the authorised authorities, MA holders and persons submitting information on the risks of pharmaceuticals concerning their impact on the patient or public health.

12. Critical Pharmacovigilance Processes

33. Critical pharmacovigilance processes include:

a) continuous monitoring of the safety profile and the risk–benefit ratio of authorised medicinal products;

b) introduction, implementation, and assessment of the risk management system (including efficiency assessment of the risk minimisation measures);

c) handling of individual case safety reports (collection, processing, management, quality control, receipt of missing data, assignment of numbers, classification, identification of repeated reports, assessment, and timely submission);

d) signal management;

e) development, preparation (including data evaluation and quality control), submission, and evaluation of periodic safety update reports;

f) fulfilling obligations and providing responses to authorised authorities' requests containing reliable and complete information;

g) ensuring interaction between pharmacovigilance and the pharmaceutical quality control system;

h) information sharing with the authorised authorities of all the safety concerns (including changes in the assessment of the risk–benefit ratio of authorised medicinal products);

i) information sharing with medical and pharmaceutical workers, patients about all changes in the assessment of the risk–benefit ratio to ensure the safe and effective use of medicinal products;

j) ensuring the compliance of the information on the medicinal product (including the summary of medicinal product characteristics) with the current level of medical knowledge, including the conclusions made on the authorised authorities' assessment and recommendations;

k) implementation of changes to the marketing authorisation application for safety-related reasons in accordance with the deadline for completing the necessary actions.

34. The process continuity plan shall be developed based on a risk-based approach and shall include:

a) determination of events that can significantly affect the personnel of the organisation in general or the structures and processes of pharmacovigilance in particular;

b) backup systems in case of an emergency exchange of information within the organisation, with other organisations performing pharmacovigilance functions, with other developers, MA holders, and the Member States' authorised authorities.

13. Functioning and Effectiveness Monitoring of the Pharmacovigilance System and Its Quality System

35. Methods for monitoring the pharmacovigilance system's activity and effectiveness shall include:

a) review and analysis of the system by responsible managers;

b) audits;

c) control of compliance with requirements;

d) inspections;

e) assessment of the effectiveness of the measures taken to minimize the risk and ensure the safe and effective use of medicinal products.

36. To carry out monitoring in the organisation, indicators must be predetermined, according to which a continuous assessment of the effectiveness of the functioning of the pharmacovigilance system in terms of quality requirements is carried out.

37. The quality system's effectiveness shall be regularly assessed by the manager who reviews the quality system documentation, the frequency and intensity determined by prior planning, reasonable risk and the developed system review programs. The quality system review shall include assessing standard operating procedures and work instructions, system performance deviations from established indicators, audit and inspection reports, and process performance indicators.

38. A risk-based quality system audit should be performed at regular intervals to confirm compliance with specified quality requirements and determine effectiveness. A quality system audit shall include an audit of the pharmacovigilance system into which the quality system is integrated. Audit methods and processes are set out in Section V of these Rules. The results of each quality system audit and subsequent audit should be followed by a report to be evaluated by those responsible for organizing the relevant audited processes. The report should include the results of the audit of organisations or persons to whom the MA holder has delegated pharmacovigilance functions since they are part of the MA holder's pharmacovigilance system.

39. Based on the pharmacovigilance system and the pharmacovigilance quality system monitoring results, including the audit results, corrective and preventive actions should be developed and implemented if necessary.

40. Authorised authorities shall ensure monitoring the fulfillment of the pharmacovigilance functions and duties by the MA holders established by the Member States' legislation. Monitoring measures include inspections of MA holders by the authorised authorities.

14. Pharmacovigilance Responsibilities of MA Holders

41. MA holders are responsible for fulfilling the tasks and responsibilities for pharmacovigilance determined by these Rules and the

Member States' legislation to guarantee the fulfillment of obligations and, if necessary, take the required pharmacovigilance activities concerning authorised medicinal products. To this end, MA holders shall ensure the functioning of the pharmacovigilance system on the Member States territories, including the implementation of an appropriate and effective pharmacovigilance quality system.

42. Under certain circumstances, it is allowed that MA holders organize more than one pharmacovigilance system, e. g. when forming a separate pharmacovigilance system for certain groups of medicinal products (in particular, vaccines, over-the-counter medications).

43. The description of the pharmacovigilance system is formed by a MA holder in the format of the pharmacovigilance system master file and is maintained throughout the entire validity period of marketing authorisations for all authorised medicinal products. A MA holder is also responsible for developing, implementing, and maintaining risk management systems adapted for each of the authorised medicinal products.

44. Requirements for the structures and processes of the MA holder's pharmacovigilance system are determined in the relevant sections of these Rules.

15. Authorised Pharmacovigilance Officer

45. In the Member States, a MA holder shall appoint and maintain at all times an authorised pharmacovigilance officer having the required qualifications. The MA holder provides the Member States' authorised authorities with the authorised pharmacovigilance officer's name and contact information. Should this information be changed, the marketing authorisation holder shall immediately, within 30 calendar days, inform the Member States' authorised authorities about this fact.

46. The authorised pharmacovigilance officer’s responsibilities shall be determined by a job description. In the organisational structure, the authorised pharmacovigilance officer’s location and interaction with other persons shall be determined at the level of the MA holder’s management personnel.

47. Information about the authorised pharmacovigilance officer must be included in the MA holder’s pharmacovigilance system master file.

48. Each pharmacovigilance system can only have one authorised pharmacovigilance officer. The authorised pharmacovigilance officer may provide services to more than one MA holder in general or specific pharmacovigilance systems, or the officer may provide services to more than one pharmacovigilance system of one MA holder, provided that the authorised pharmacovigilance officer can perform all own responsibilities. In addition to the appointment of an authorised pharmacovigilance officer, authorised authorities may require the assignment of a contact person for pharmacovigilance accountable to the authorised pharmacovigilance officer. Accountability here refers to pharmacovigilance tasks and responsibilities and does not necessarily mean direct subordination. The contact person is entitled to act as an authorised pharmacovigilance officer. The MA holder’s pharmacovigilance system organisation on the Member State territory shall ensure compliance with the requirements of the Union authorities’ acts and the Member States’ legislation in the field of pharmacovigilance, effective interaction with the authorised authority and the absence of obstacles in the collection and submission of information on identified adverse reactions on the Member State territory.

49. The MA holder grants the authorised pharmacovigilance officer sufficient authority to manage the pharmacovigilance activity and the quality system. The MA holder provides the authorised pharmacovigilance officer

with access to the pharmacovigilance system master file and the appropriate powers and ensures that information is received about any changes in the pharmacovigilance system master file. The authority for the pharmacovigilance system and the pharmacovigilance system master file shall allow the authorised pharmacovigilance officer to make changes to the system, risk management plans, and prepare regulatory actions in response to any emerging safety issue identified.

50. The MA holder ensures that all systems and processes are in place to enable the authorised pharmacovigilance officer to perform the assigned duties. To this end, the MA holder develops mechanisms by which the authorised pharmacovigilance officer has access to all the data that he/she may need and receives all the necessary information, for example:

a) information on emerging safety issues related to changes in the safety profile and other information regarding the assessment of the risk–benefit ratio of medicinal products covered by the pharmacovigilance system;

b) information on ongoing and completed clinical trials and other studies that the MA holder knows about and that may be relevant to the safety of medicinal products;

c) information received from sources other than those of the MA holder (e. g., sources with which the MA holder has contractual agreements);

d) information on the procedures relevant for pharmacovigilance that the MA holder develops at each level to ensure consistency and compliance with the requirements within the organisation.

51. The authorised pharmacovigilance officer receives information from the management personnel on the results of continuous reviews of the quality system and the measures taken, data on compliance with the requirements, planned pharmacovigilance system audits. The authorised pharmacovigilance officer has the authority to initiate an audit if necessary.

52. After each audit of relevance for the pharmacovigilance system, the management personnel provide the authorised pharmacovigilance officer with a copy of the corrective and preventive action plan so that the authorised pharmacovigilance officer can be sure that the appropriate corrective action is being taken.

53. The MA holder provides an opportunity for the authorised pharmacovigilance officer to receive information from the adverse reactions database at his disposal at any time in case of need for an immediate response to an urgent request from the authorised authority. The MA holder shall take appropriate organisational measures that allow the authorised pharmacovigilance officer to access the adverse reactions database, including outside working hours.

54. The MA holder ensures that the authorised pharmacovigilance officer is informed about the intentions to include additional medicinal products in the existing list by acquiring another company or individual medicinal products from another MA holder. The authorised pharmacovigilance officer evaluates the possible impact of the inclusion of new medicinal products on the current pharmacovigilance system, ensures the necessary adaptation of the pharmacovigilance system, and determines the pharmacovigilance data that must be provided by the former MA holder and the time frame for submission. The MA holder ensures that the authorised pharmacovigilance officer is informed about the parties' contractual obligations in terms of pharmacovigilance activities and the safety data exchange and gives them the right to amend this part of the contractual obligations. The authorised pharmacovigilance officer informs the MA holder if it is necessary to implement additional conditions to ensure the proper fulfillment of pharmacovigilance obligations concerning these medicinal products, the possibility of fulfilling these pharmacovigilance

obligations shall be taken into account when making a decision and determining the contractual obligations of the parties.

55. The MA holder ensures that the authorised pharmacovigilance officer is informed about the intention to establish cooperation with another MA holder, an organisation, or an individual who may directly or indirectly influence the pharmacovigilance system, before entering into contractual arrangements within the time sufficient for the authorised pharmacovigilance officer to perform the assessment the possible impact of this collaboration on the pharmacovigilance system. The MA holder empowers the authorised pharmacovigilance officer to make proposals and changes in contractual obligations related to the pharmacovigilance system.

16. The Authorised Pharmacovigilance Officer's Qualifications

56. The authorised pharmacovigilance officers shall have theoretical knowledge and practical experience in pharmacovigilance activities; their level of competence is determined by the MA holder in the job description of the authorised pharmacovigilance officer. The authorised pharmacovigilance officer shall have the skills to manage pharmacovigilance systems and conduct expertise or have access to expertise in such fields as medicine, pharmaceutical sciences, epidemiology, and biostatistics.

57. The MA holder conducts training for the authorised pharmacovigilance officer in the area of his/her pharmacovigilance system before the authorised pharmacovigilance officer's appointment. The training and its results must be properly documented.

17. Authorised Pharmacovigilance Officer's Functions

58. An authorised pharmacovigilance officer is a natural person.

59. The authorised pharmacovigilance officer shall be qualified in accordance with paragraphs 56 and 57 of these Rules and be at the permanent MA holder's disposal. The person authorised to perform the functions of an authorised pharmacovigilance officer on the Member States territories shall reside and work in one of the Member States. The MA holder shall ensure that there are backup procedures in case of the temporary absence of the authorised pharmacovigilance officer, with the definition of the person performing the authorised pharmacovigilance officer's duties in his/her absence. The MA holder shall ensure that the person substituting the authorised pharmacovigilance officer can fulfill the pharmacovigilance duties. In this case, the substituting person shall be available when using the contact details of the authorised pharmacovigilance officer.

60. The authorised pharmacovigilance officer is responsible for the creation and operation of the MA holder's pharmacovigilance system and, therefore, has sufficient powers to influence the implementation of pharmacovigilance activities and the pharmacovigilance quality system, to promote, comply with and improve the level of compliance with the requirements of the legislation of the Member States, international treaties and acts constituting the right of the Union. The authorised pharmacovigilance officer shall have the authority and responsibility for the pharmacovigilance system master file in order to ensure and increase the level of compliance with the requirements of the Union authorities' acts and the Member States' legislation.

61. For medicinal products covered by the MA holder's pharmacovigilance system, the authorised pharmacovigilance officer shall:

a) have an overview of medicinal product's safety profiles and identified safety concerns;

b) be fully informed about the conditions and obligations established when issuing marketing authorisation and other obligations related to the medicinal product safety or safe use.

c) have full knowledge of risk minimisation measures;

d) take part in the assessment and approval of the protocols of post-authorisation safety studies.

e) have complete information on post-authorisation safety studies, the conduct of which is appointed by the authorised authority, including the results of such studies;

f) have information about the content of risk management plans and have sufficient authority to make changes to risk management plans;

g) ensure that pharmacovigilance functions are performed and the all documents related to pharmacovigilance are submitted in accordance with the requirements of the Union authorities' acts and the Member States' legislation;

h) ensure the required quality (including accuracy and completeness) of pharmacovigilance data submitted to the authorised authorities;

i) ensure complete and timely submission of responses to authorised authorities' requests for the provision of additional information necessary to assess the benefits and risks of medicinal products;

j) submit any information related to the assessment of the risk–benefit ratio to the authorised authorities;

k) assist in the preparation of regulatory actions when any safety concerns are identified (e. g., changes in recommendations for medical use, urgent restrictions, and notification of patients and healthcare professionals);

l) function as a single contact person in pharmacovigilance for the Member States' authorised authorities and a contact person for pharmacovigilance inspections, ensuring round-the-clock (24-hour) access of

the authorised authority to the authorised person in pharmacovigilance. The authorised pharmacovigilance officer monitors the functioning of all aspects of the pharmacovigilance system, including its quality system (e. g., standard operating procedures, contractual agreements, database operations, compliance with quality system requirements, compliance with data reporting requirements in terms of completeness and timeliness, submission of periodic safety update reports, audit reports, and pharmacovigilance training). The authorised pharmacovigilance officer shall possess information on the validation status of the adverse drug reactions database, including any deficiencies identified during validation and corrective actions taken), as well as information on any significant changes made to the database (e. g., changes that may impact the pharmacovigilance activities).

62. The authorised pharmacovigilance officer is entitled to delegate the implementation of specific tasks under his/her supervision to persons with appropriate qualifications and training (e. g., acting as experts on the safety of certain medicinal products) provided that the authorised pharmacovigilance officer will monitor the functioning of the entire system and the safety profiles of all medicinal products. Such delegation of functions to be performed shall be properly documented.

18. Specific Quality System Processes from Marketing Authorisation Holders

63. A marketing authorisation holder develops additional specific quality system processes with a view to:

a) submitting data on adverse reactions to databases of the Member States and a unified information database on identified adverse reactions (actions) to medicinal products, including reports of medicinal product

ineffectiveness within the time limits established by the Union authorities' acts and the Member States' legislation;

b) systematically or regularly monitoring the terminology used;

c) saving the pharmacovigilance system master file documents as long as the system described in the pharmacovigilance system master file operates and for at least 5 years after its termination;

d) saving pharmacovigilance data and documents related to authorised medicinal products for at least 10 years after termination of the authorisation;

e) updating information on medicinal products following the latest scientific knowledge (including an assessment of the safety profile and the risk–benefit ratio) and the recommendations posted on the authorised authorities' websites in the information and telecommunications network "Internet" (hereinafter referred to as the Internet). To this end, the MA holder constantly checks the websites of the Member States' authorised authorities for relevant changes in the assessment of the safety profile and the risk–benefit ratio, including changes in recommendations for medical use and other regulatory measures.

64. During the storage period of the documents, marketing authorisation holders ensure the recoverability of documents.

65. Documents can be stored in electronic format, provided that the electronic system is properly validated and agreements exist to protect the system, access, and backup data. In the case of adapting documents from hard copy to electronic format, it must ensure that all information is preserved in the original format and ensure that readability is maintained throughout the entire storage period by the means used for storage.

66. In the event of a takeover by another organisation of the marketing authorisation holder's business, all documents must be transferred and retained in full.

19. Requirements for the Quality System when Delegating the Performed Pharmacovigilance Tasks by the Marketing Authorisation Holder

67. A marketing authorisation holder is entitled to delegate all or part of his/her pharmacovigilance tasks (including the authorised pharmacovigilance officer's functions) to another organisation or person (if the exact requirements can be applied to such a person as to the organisation). At the same time, the MA holder is responsible for fulfilling tasks and obligations for pharmacovigilance, quality assurance, and the integrity of the pharmacovigilance system.

68. When delegating certain pharmacovigilance tasks to another organisation, the marketing authorisation holder is responsible for applying an effective quality system for the execution of these tasks. The pharmacovigilance system requirements as defined by Good Pharmacovigilance Practice also apply to this organisation.

69. When delegating tasks to another organisation, a marketing authorisation holder provides detailed, precise, and constantly updated documentation of the contractual agreements between it and the other organisation, describing the arrangements for delegated tasks and each other's responsibilities. A description of delegated tasks shall be included in the pharmacovigilance system master file (with indication of contracting organisations in the attachment to the master file). Another organisation is subject to inspection for compliance with the performed pharmacovigilance activities in accordance with the requirements of these Rules at the discretion of the authorised authority.

70. Contractual arrangements for delegated pharmacovigilance tasks shall ensure that the parties comply with the requirements of the Union authorities' acts and the Member States' legislation relating to pharmacovigilance. A marketing authorisation holder must ensure that the

contract includes a detailed description of the tasks delegated, the method of interaction and exchange of data, time obligations, the terminology used, the maintenance of databases, monitoring of the activities performed, and other aspects necessary for the proper performance of the delegated tasks. In order to monitor compliance with contractual arrangements, the marketing authorisation holder should perform regular audits of organisations to which pharmacovigilance tasks have been delegated.

20. General Pharmacovigilance Responsibilities within the Framework of the Union Authorities' Acts

71. The authorised authorities are responsible for fulfilling the pharmacovigilance tasks assigned to them by the Union authorities' acts and the Member State's legislation. To this end, each authorised authority ensures the pharmacovigilance system's functioning, creates and applies an appropriate, effective quality system for the pharmacovigilance activities performed.

72. Member States shall collaborate to continuously improve pharmacovigilance systems and achieve high standards of public health (health of population) protection, including the use of pooled resources to optimize the use of available resources within the Union.

73. Member States define contacts to simplify the interaction of the authorised authorities, MA holders, and persons submitting pharmacovigilance information.

21. Authorised Authorities' Functions

74. Each Member State shall designate an authorised authority responsible for the implementation of pharmacovigilance activities.

75. Each authorised authority shall implement and ensure the effective functioning of the pharmacovigilance system in the performance of its tasks and participation in pharmacovigilance activities within the Union. In this context, the authorised authority is responsible for monitoring each authorised medicinal product's safety, regardless of the authorisation procedure applied.

76. The tasks and responsibilities of the authorised authorities for pharmacovigilance include cooperation in the detection of signals and the application of risk minimisation measures when making appropriate decisions. If it is necessary to take urgent measures to ensure the protection of public health (health of the population) concerning a medicinal product authorised in compliance with the mutual recognition procedure, the authorised authority of the Member State concerned takes the necessary steps, including withdrawal from the market or stopping use in the territory of its state.

77. Authorised authorities are responsible for monitoring the fulfillment by MA holders of their pharmacovigilance obligations for medicinal products in the territory of their states, including inspections of the MA holders' pharmacovigilance systems, regardless of the authorisation procedure for medicinal products in the Member States' territories. The authorised body of one Member State ensures that pharmacovigilance data are submitted to the authorised authorities of other Member States in accordance with the acts of the Union authorities and the Member States' legislation.

22. Pharmacovigilance Preparedness Planning in case of Public Health Emergencies

78. Pharmacovigilance systems of marketing authorisation holders and the Member States' authorised authorities shall be adapted to public health emergencies, including the development of an emergency preparedness plan.

79. A public health emergency is a threat to public health (health of population) recognised by the World Health Organisation or authorised authorities.

80. The requirements for the pharmacovigilance system in case of public health emergencies in each of the cases are determined by the authorised authorities and are communicated to the marketing authorisation holders and the public. Authorised authorities publish emergency notifications on their official websites on the Internet.

III. Pharmacovigilance System Master File

1. Structure of the Pharmacovigilance System Master File

81. The pharmacovigilance system master file is intended to describe the pharmacovigilance system and provide documentary evidence of its compliance with the requirements of the Union authorities' acts and the Member States' legislation. The pharmacovigilance system master file allows properly planning and conducting the pharmacovigilance system audits by a marketing authorisation holder and inspections by the authorised authorities. The pharmacovigilance system master file includes an overview of the marketing authorisation holder's pharmacovigilance system, making it possible to make its general assessment by the authorised authorities while getting the marketing authorisation and at the post-authorisation period.

82. Drawing up a pharmacovigilance system master file and updating the information contained in it allow a marketing authorisation holder and the authorised pharmacovigilance officer for the following:

a) making sure that the pharmacovigilance system is implemented in accordance with the requirements of the Union authorities' acts and the Member States' legislation;

b) confirming the compliance of the system with the current requirements;

c) obtaining information about system deficiencies or identify non-compliance with requirements;

d) obtaining information about the risks or ineffectiveness of the implementation of certain pharmacovigilance activity areas.

83. The use of the pharmacovigilance system master file helps to optimize the process of proper system management and improve the pharmacovigilance system. The requirements for the submission of a summary of the marketing authorisation holder's pharmacovigilance system, the submission of the pharmacovigilance system master file, and the chronology (sequence) of changes facilitate the planning and effective conduct of inspections by the authorised authorities of the Member States based on the risk assessment method.

2. Approving and Keeping a Pharmacovigilance System Master File Up to Date

Brief Description of the Marketing Authorisation Holder's Pharmacovigilance System.

84. In accordance with the requirements of the Rules for Marketing Authorisation and Expert Assessment, a brief description of the marketing authorisation holder's pharmacovigilance system is provided in Section 1.10 of Module 1 of the marketing authorisation application for a medicinal product in the event that when previously submitting the Marketing Authorisation Application, the marketing authorisation holder submitted to

the authorised authority the pharmacovigilance system master file of the marketing authorisation holder. The summary of a pharmacovigilance system shall include the following elements:

a) a written confirmation by the marketing authorisation holder that there is an authorised pharmacovigilance officer;

b) information on a Member State where the authorised pharmacovigilance officer lives and performs his (her) functions;

c) contact details of the authorised pharmacovigilance officer and the contact person for pharmacovigilance (if any);

d) declaration signed by the marketing authorisation holder committed to performing activities and obligations listed in the Rules of the Good Pharmacovigilance Practice of the Union;

e) location (address) of the pharmacovigilance system master file.

Location Requirements for the Pharmacovigilance System Master File

85. A pharmacovigilance system master file shall be stored in the territory of a Member State either at the place where the marketing authorisation holder actually carries out his/her core pharmacovigilance activity, or at the address of the main place where the pharmacovigilance authorised person carries out his/her activity, regardless of the format of this master file (in paper or electronic form). The Member State's authorised authority shall be informed about the storage location of the pharmacovigilance system master file and must immediately, within up to 30 days, be notified of any changes in its storage location. The required information on the master file location includes an indication of the location (address) of the marketing authorisation holder or a third party pursuant to the agreement. This location (address) may differ from the applicant's or the

marketing authorisation holder’s location (address), for example, if the location (address) of another marketing authorisation holder’s office is indicated or a third party performs the main activity pursuant to the agreement. When determining the main location for the pharmacovigilance activity, the marketing authorisation holder shall determine the best location for the pharmacovigilance system as a whole to ensure the pharmacovigilance system functioning. The marketing authorisation holder shall have appropriate justification for deciding on the location of the master file. In a situation where the main activity is carried out in third countries, or it is impossible to determine the main location, by default, the storage location of the master file is the place of business of the authorised pharmacovigilance officer.

Transfer of Responsibilities for Maintaining the Pharmacovigilance System Master File

86. The transfer of responsibilities for maintaining the pharmacovigilance system master file should be documented and monitored to confirm that a marketing authorisation holder fulfills his/her duties. The authorised pharmacovigilance officer shall be notified of any changes made to the pharmacovigilance system master file, including immediately of the following changes:

a) changes made to a pharmacovigilance system master file, or a change in its location, information about which must be reported to the authorised authorities of the Member States;

b) adding information on corrective and/or preventive measures to the pharmacovigilance system master file (e. g., based on the audit and inspection results). The authorised pharmacovigilance officer shall have

access to information about deviations from processes identified in the quality management system of the pharmacovigilance system;

c) changes made to the information contained in the master file that meet the criteria for proper control of the pharmacovigilance system (within the framework of the system's capabilities, functioning, and compliance with the requirements);

d) changes in the established agreement on the submission of the pharmacovigilance system master file to the authorised authorities;

e) transferring the performance of a significant pharmacovigilance function to a third party (e. g., the development of pharmacovigilance documents);

f) inclusion of medicinal products in the pharmacovigilance system, for which the authorised pharmacovigilance officer is responsible;

g) changes concerning medicinal products included in the pharmacovigilance system, which may require an increase in the number of pharmacovigilance activities performed (e. g., addition of indications, implementation of studies, inclusion of additional countries).

87. The authorised pharmacovigilance officer shall confirm in writing that they have assumed the responsibility for maintaining the pharmacovigilance system master file.

5. Pharmacovigilance System Description

88. The pharmacovigilance system master file shall describe the MA holder's pharmacovigilance system for one or more medicinal products. The MA holder is entitled to apply different pharmacovigilance systems to different categories of medicinal products. Each such system shall be described in a separate pharmacovigilance system master file. The pharmacovigilance system master file shall jointly cover all medicinal

products of the MA holder for which the marketing authorisation has been issued.

89. If the MA holder has more than one pharmacovigilance system, for example, specific pharmacovigilance systems for certain types of medicinal products (vaccines, sanitary and hygienic products, etc.), or the pharmacovigilance system covers medicinal products from more than one of the MA holders, a separate pharmacovigilance system master file describing each system shall be drawn up.

90. The MA holder shall appoint an authorised pharmacovigilance officer responsible for creating and maintaining the pharmacovigilance system described in the pharmacovigilance system master file.

91. If several MA holders use one pharmacovigilance system, each of them is responsible for the availability of a pharmacovigilance system master file, which describes the pharmacovigilance system for its products. The MA holder may delegate, through a written agreement (e. g., to a license partner or subcontractor), part or all of the pharmacovigilance tasks for which the MA holder is responsible. In this case, the MA holder's pharmacovigilance system master file may have a cross-reference to the master file or to a part of the pharmacovigilance system master file managed by the system of the party to which the tasks were delegated following an agreement on access to this information by the MA holder and authorised authorities of the Member States. The MA holder shall ensure that the reference files' content complies with the pharmacovigilance system applicable to the medicinal product.

92. Where appropriate, the annex shall contain a list of pharmacovigilance system master files supported by one MA holder. The attached information includes data on the location of the master files, information about the authorised pharmacovigilance officer and related medicinal products.

93. It is not allowed to indicate several storage locations of one pharmacovigilance system master file in the summary information submitted to the Member States' authorised authorities.

94. The authorised pharmacovigilance officer's data may be the data of the person whom the MA holder authorised to perform the pharmacovigilance system management functions based on the contractual agreement and who is not a direct employee of the MA holder.

95. When delegating the pharmacovigilance tasks, the MA holder is responsible for the pharmacovigilance system, providing information on the pharmacovigilance system master file's location, maintaining the pharmacovigilance system master file, and submitting it to the Member States' authorised authorities upon request. There shall be agreements describing the roles and responsibilities for maintaining and submitting the pharmacovigilance system master file and exercising pharmacovigilance in accordance with the requirements of the Member State's legislation.

96. When using a pharmacovigilance system by several MA holders, it is recommended that partners agree on joint maintenance of the relevant sections within their master files in the system. The availability of the pharmacovigilance system master file for MA holders and its submission to the Member States' authorised authorities shall be specified in agreements. It is important for the MA holder to make sure that the pharmacovigilance system for his/her products meets the necessary requirements.

4. Mandatory Information in the Pharmacovigilance System Master File

97. A pharmacovigilance system master file shall include documents describing the pharmacovigilance system. The pharmacovigilance system master file's content shall reflect the availability of safety information of

medicinal products authorised in the Member States. The master file shall have a table of contents for navigation in the document. The main principle of forming the structure of the content of the master file is the inclusion of information in the main sections, which is fundamental for the description of the MA holder's pharmacovigilance system. It is allowed to include some detailed information required for a complete description of the system can be included in the annexes to the pharmacovigilance system master file, as this data is subject to frequent changes.

Master File Section on the Authorised Pharmacovigilance Officer

98. Information about the authorised pharmacovigilance officer in a pharmacovigilance system master file shall include:

a) description of the responsibilities to ensure that the authorised pharmacovigilance officer has appropriate authority over the pharmacovigilance system to ensure, assist and improve compliance.

b) summary with core information on the role of the authorised pharmacovigilance officer, description of his/her qualifications, and experience with pharmacovigilance activities.

c) the authorised pharmacovigilance officer's contact information (last name, first name, patronymic (if any), phone numbers, fax numbers, e-mail address and work place location (address), indicating the postal code);

d) information on the use of agreements in the absence of the authorised pharmacovigilance officer. Should any specific tasks of the authorised pharmacovigilance officer be delegated to another performer, the list of delegated tasks shall be included in the annexes (indicating the description of the tasks delegated and the persons to whom they have been delegated);

e) description of the responsibility area of the contact pharmacovigilance person (if any).

The Pharmacovigilance System Master File Section on the MA Holder's Organisational Structure

99. It is necessary to describe the organisational structure of the relevant pharmacovigilance system of a MA holder. The description shall give a clear idea of the organisations involved, the main structural units involved in pharmacovigilance, and the relationship between organisations and structural units related to the performance of pharmacovigilance activities. The pharmacovigilance system master file shall provide the following information:

a) the MA holder's organisational structure, including information on the authorised pharmacovigilance officer's position in the organisation;

b) location (address) at which pharmacovigilance activities are carried out, including the collection and assessment of adverse reaction reports, entering reports into the safety database, preparing a periodic safety update report, identifying and analyzing signals, maintaining risk management plans, managing pre-authorisation and post-authorisation studies, and managing the changes made to the safety information of a medicinal product.

The Pharmacovigilance System Master File Section on Delegated Pharmacovigilance Activities

100. The pharmacovigilance system master file shall contain a description of the pharmacovigilance tasks delegated by the MA holder.

101. The information in the section shall contain confirmation of the relationship with other organisational structures (e. g., an agreement on joint marketing of a medicinal product, an agreement on the pharmacovigilance

activities implementation by contractors, as well as other commercial agreements). It is necessary to locate and describe the system of existing agreements for delegated pharmacovigilance tasks. The agreement description may be compiled in the form of a list or a table. When describing the agreements in the form of a table, information is provided on the parties concerned, the obligations undertaken, medicinal products for which pharmacovigilance is performed, and the Member States territory where pharmacovigilance is conducted. When describing the agreements in the form of a list, it shall be structured by the types of services used (e. g., the provision of medical information, audit services, provision of patient support programs, study data processing), types of commercial agreements (medicinal product distribution agreement, joint marketing agreement, agreement on the joint rights to a marketing authorisation, etc.) and types of technical support for pharmacovigilance activities (placing computerised systems on the provider’s servers, archiving and storing pharmacovigilance data, etc.). Copies of individual agreements are submitted at the request of the authorised authorities or during the inspection and audit; their list is provided in the annexes to the master file.

The Master File Section on Safety Data Sources

102. The description of the main pharmacovigilance system departments engaged in collecting the adverse reaction reports shall include information on all parties responsible for collecting solicited and spontaneous reports of adverse reactions to a medicinal product authorised in the Member States territories. The description shall include the location of the health information departments and the affiliated offices of the organisation. This information may be compiled in the form of a list indicating the state, the nature of the activity, and medicinal products (if this activity depends on the

type of medicinal product). Information about third parties (license partners, partners in local distribution or marketing agreements) is also included in the section describing the agreements. Diagrams can be used to represent the main steps involved in collecting and communicating adverse reaction data, timing, and parties involved. The description of the process for individual reports on adverse reactions from collection to submission to the authorised authority shall include information on the units and/or third parties involved in the procedure.

103. Sources of safety information shall also include a list of ongoing studies, registries, support programs, or observational studies sponsored by a MA holder in which individual case safety reports may be submitted. MA holders shall be able to provide these lists upon request when conducting pharmacovigilance system inspections, audits, or the system assessment performed by the authorised pharmacovigilance officer. The list shall describe the status of each study or program (with account for its worldwide implementation), the respective state, medicinal products and main targets. Interventional and non-interventional studies shall be indicated separately according to the active ingredient of the medicinal products. The list shall contain all studies (programs), ongoing studies (programs), as well as studies (programs) completed within the last 2 years, and can be included in the annex to the pharmacovigilance system master file, or submitted upon request.

It should be considered that non-interventional studies are defined by the methodological approach used, not the scientific objectives. Non-interventional studies include database analyses or medical record reviews, that have already described all of the events under consideration (in particular, case-control studies, crossover and cohort studies), as well as studies that involve primary data collection (in particular, prospective non-

interventional studies, studies based on registries that record the data obtained for a routine treatment process) when the above conditions are met. Non-interventional studies include interviewing, questioning, and blood sampling may be conducted as part of routine clinical practice.

The Master File Section on Computerised Systems and Databases

104. The pharmacovigilance system master file shall describe the location, functionality, and responsibility for operating the computerised systems and databases used to obtain, verify, report safety information and assess its compliance with the assigned tasks.

105. If several computerised systems or databases are used, their applicability to pharmacovigilance activities shall be described in such a way that the scope of computerisation (degree of information technology implementation) within the pharmacovigilance system is understood. Besides, the validation status of the main aspects of the functionality of the computerised system, as well as the control of changes, the test structure, backup procedures, and electronic data archives necessary for compliance with pharmacovigilance requirements, and the available documentation shall be described. For hard copy filing systems (where the electronic system is used only for the urgent submission of individual case safety reports), it is necessary to describe the data management, the mechanisms used to ensure the integrity and access to the data, and the inclusion of information about adverse drug reactions in the signal detection procedure.

The Master File Section on Processes

106. An important component of the pharmacovigilance system is the availability of written standard procedures at the place of pharmacovigilance

activity implementation. Section II of these Rules describes the minimum set of such pharmacovigilance procedures.

107. The pharmacovigilance system master file shall describe the available documentation on written standard procedures (references to specific standard operating procedures, manuals, etc.), data types (e. g., the type of data on individual cases of adverse reactions), and the way records are maintained (e. g., a safety database, hard copies).

108. The pharmacovigilance system master file shall include a description of the processes, procedures for processing, and recording data when performing pharmacovigilance activities, which shall include the following aspects:

a) continuous monitoring of the risk–benefit ratio of the medicinal product, the result of the assessment, and the process of deciding on appropriate measures, the process of identifying, validating, and evaluating signals, obtaining safety results, exchanging data with departments involved in the medical and scientific assessment of safety data, etc.;

b) description of risk management system and monitoring of the results of the implementation of risk minimisation measures. If several departments are involved in this process, the order of their interaction is determined by documented procedures or agreements;

c) collection, verification and obtaining follow-up information, assessment, and presentation of information on individual cases of adverse reactions. Description of procedures in this section shall clearly distinguish between local and international activities;

d) planning, drawing up and submitting periodic safety update reports;

e) providing consumers, healthcare professionals, and authorised authorities with information on safety concerns;

f) making safety-related changes in the summary of product characteristics and the patient information leaflet. The description of procedures shall include the internal and external exchange of pharmacovigilance system data.

109. For each line of business, a MA holder shall be able to confirm the functioning of his/her system for making timely appropriate decisions and actions.

110. Data on other activities shall be provided to demonstrate that, within the pharmacovigilance system, an adequate quality assurance system exists. To such data, in particular, data on the functions and responsibilities of an authorised pharmacovigilance officer, response to the authorised authorities' requests for information, analysis of publications in scientific medical literature, control of changes in safety databases, agreements on the exchange of safety data, archiving safety data, pharmacovigilance audit, quality system control, and training. The list of procedures that may be included in the Annexes to the pharmacovigilance system master file shall include the number, title, effective date, and type of document (for all standard operating procedures, work instructions, manuals, etc.). Procedures that have been delegated to third persons shall be properly identified. Documents related to specific local procedures may not be included in the general list of procedure documents but must be provided at the authorised authority's request (indicating the states in which these procedures are used).

The Master File Section on the Pharmacovigilance System Functioning

111. The pharmacovigilance system master file shall include confirmation of continuous monitoring of the functioning of the

pharmacovigilance system, including the control of the main results, as well as a description of the monitoring methods and at least contain:

description of the procedure for assessing the correctness of the submission of individual case safety reports, including drawings (graphs) confirming the timeliness of the information submission in compliance with the Member States' legislation requirements;

description of the performance indicators used to control the quality of the information provided and pharmacovigilance activities. Such indicators include information from the authorised authorities on the quality of the adverse reaction reports, the periodic safety update report and other data submitted;

analysis of the timeliness of submission a periodic safety update report to the Member States' authorised authorities (an annex to the master file shall reflect the latest data used by the MA holder to assess compliance with the Member States' legislation requirements);

analysis of the methods used to assess the timeliness of making changes related to safety subject to the deadlines established by the authorised authorities, including the method of monitoring the introduction of necessary changes that have been identified but information about which has not yet been submitted to the authorised authority;

where appropriate, an analysis of the fulfillment of obligations following the risk management plan or other obligations or requirements established during authorisation and related to pharmacovigilance.

The objectives of the effective functioning of the pharmacovigilance system should be described and explained. Where appropriate, a list of performance indicators for pharmacovigilance activities should be attached to the pharmacovigilance system master file.

The Master File Section on the Quality System

112. The section describes the quality management system within the scope of the organisation and the application of the pharmacovigilance quality system.

Control of Documents and Records

113. In terms of document and record control, a description of the archiving mechanisms for electronic and/or hard copy versions of the pharmacovigilance system master file shall be provided, and an overview of the procedures applied to other records documents of the pharmacovigilance quality system.

Procedure Documents

114. The procedure documents description shall include:

a) general description of the types of documents used in the pharmacovigilance system (standards, work procedures, work instructions, etc.), an indication of the applicability of various documents at the global, regional, or local level of the functioning of the pharmacovigilance system in the organisation, as well as the elements of document control that are applied in regarding access to procedure documents, implementation, and maintenance;

b) information on the documentation system applied to procedure documents controlled by third parties.

Personnel Training

115. During pharmacovigilance activities, a resource management description shall be provided, including the following:

organisational structure with indication of the number of people involved in pharmacovigilance activities (in staffing positions), which can be presented in a separate section describing the organisational structure;

information on the location of the personnel arranging and implementing certain types of pharmacovigilance activities (provided in the pharmacovigilance system master file and its annexes) and contact persons who submit safety data. Information on the personnel location shall include an indication of the scope of pharmacovigilance activities and activity locations in order to justify the training arrangement system;

a summary of the training context, including a link to where the training records are kept.

Personnel shall be appropriately trained to carry out pharmacovigilance activities. This applies not only to personnel in pharmacovigilance units but also to persons who may receive safety reports.

Audit

116. Information about the audit of the quality assurance system in the pharmacovigilance system shall be included in the pharmacovigilance system master file. The annex should include a description of the pharmacovigilance system audit scheduling method and reporting mechanisms and a list of planned and completed pharmacovigilance system audits. This list shall include the dates of audits and submission of reports on the results of audits, the scope and status of audits by service providers, separate pharmacovigilance activities or locations of pharmacovigilance functions, and interaction areas of these subdivisions or structures relevant to meeting obligations. The list shall include data covering a 5-year period. In cases where the MA holder’s pharmacovigilance system has existed for less than 5 years, the list may include data for the relevant period.

117. The pharmacovigilance system master file shall also contain comments on audits, during which significant results were obtained. This means that the list of audits performed shall indicate the assessed results as significant or critical inconsistencies and a summary of the corrective or preventive action plan for these inconsistencies with performance deadlines. Reference shall be made to the full audit report, documents with the corrective and preventive action plan shall be attached. Where the corrective and preventive action plan for a specific audit or non-conformity has not been agreed as of the date of the listing, an appropriate comment shall be added (“the corrective and preventive action plan(s) shall be agreed”). In the annex, in the list of audits performed, audits with pending approval work shall be indicated. Comments and related information on corrective and preventive actions shall be included in the pharmacovigilance system master file until corrective and /or preventive actions are fully implemented; thus, comments are deleted only after they have been demonstrated the results of the implementation of corrective actions and/or the confirmation (including from an independent party) of significant system improvement is provided. Adding, changing, or removing comments shall be recorded in the appropriate logbook.

118. As a means of managing the pharmacovigilance system and providing the basis for an audit or inspection, the pharmacovigilance system master file shall also contain a description of the processes for registering, processing, and eliminating deviations identified in the quality management system. The master file also includes data on the detected deviations of the performed pharmacovigilance procedures, the results of evaluating the impact of deviations, and managing deviations until they are entirely eliminated. Deviation handling information may be included in the form of a

list with indication of report numbers, deviations, dates, and a description of the relevant procedures performed.

Annex to the Pharmacovigilance System Master File

119. The annex to the pharmacovigilance system master file shall contain the following documents:

a) a list of medicinal products authorised by a MA holder in the Member States and in third states to which the pharmacovigilance system master file applies, including the trade names of medicinal products, international non-proprietary names of active ingredients, and the name of the state in which the marketing authorisation is valid.

The list of medicinal products approved in the Member States shall include the marketing authorisation number and the following information for each certificate of marketing authorisation:

type of authorisation procedure (e. g., authorisation of a medicinal product under the Member State's legislation through a mutual recognition procedure or a decentralised procedure);

reference Member State;

presence in the Member States' markets.

third countries in whose territories the medicinal product is authorised or in whose markets it circulates.

The list shall be structured by active ingredients and, where appropriate, shall contain an indication of the existence of specific requirements for the safety control of the medicinal product (e. g., the introduction of risk minimisation measures described in the risk management plan or established as a condition for the medicinal product authorisation, change in the frequency of submitting the periodic safety update report; inclusion in the list of drugs subject to additional monitoring).

For marketing authorisations that are included in another pharmacovigilance system, if a MA holder has more than one pharmacovigilance system or has an agreement with a third party to delegate pharmacovigilance tasks for this marketing authorisation, the pharmacovigilance system master file shall include a link to an additional pharmacovigilance system master file in the form of a separate list in the annexes to provide complete information on master files for all medicinal products of the MA holder.

Where joint pharmacovigilance systems are used, all medicinal products covered by the pharmacovigilance system described in the pharmacovigilance system master file must be included in the list of medicinal products. To submit this information, one list can be used with indication of the MA holder(s)' name for each medicinal product, or, alternatively, separate lists describing the medicinal products of each of the MA holders;

b) a list of standards and quality system procedures for the pharmacovigilance system;

c) a list of contractual arrangements to delegate pharmacovigilance activities, including relevant medicinal products and territories;

d) a list of tasks delegated by the authorised pharmacovigilance officer;

e) a list of audits completed over a 5-year period and planned audits. In cases where the MA holder's pharmacovigilance system has existed for less than 5 years, the list may indicate data for the relevant period;

f) a list of indicators for assessing pharmacovigilance activities (where applicable);

g) a list of other pharmacovigilance system master files maintained by the MA holder (where applicable).

The list should include the number of the pharmacovigilance system master file and information about the authorised pharmacovigilance officer responsible for this pharmacovigilance system. Where this pharmacovigilance system is operated by another party that is not the MA holder, information on this pharmacovigilance service provider is indicated;

h) a log of all changes made to the pharmacovigilance system master file content for the last 5 years, except for information specified in indents 3 to 6 of paragraph 99 of these Rules and information included in the annexes to the pharmacovigilance system master file. The information on changes shall include the change date, data on the person responsible for the change, and a description of the change made.

5. Change Control, Versioning, and Archiving

120. MA holders shall ensure that the change management system is applied in the pharmacovigilance system master file and use reliable processes for timely obtaining the information on relevant changes and subsequent proper master file updating. Authorised authorities may request information on important changes in the pharmacovigilance system, which particularly may include the following:

changes in the pharmacovigilance system safety database(s), which may include changes in the database itself or interconnected databases, changes in the database validation status, and changes in information about data transmitted or transferred;

changes in the provision of significant pharmacovigilance services, especially regarding important contractual agreements for the safety data submission;

such organisational changes as the takeover of one company by another, merger, change of place of implementation of pharmacovigilance

activities, or delegation (transfer) of management of the pharmacovigilance system master file.

In addition to documenting changes in the master file (in the registration log), the MA holder shall ensure that the authorised pharmacovigilance officer is informed about these changes.

121. Changes in the pharmacovigilance system master file shall be documented with a history of changes (indicating the date and description of the change) in the changelog. The changelog includes information on all changes made to the content of the pharmacovigilance system master file, except for information specified in indents 3 to 6 of paragraph 99 of these Rules and the information included in the annexes of the pharmacovigilance system master file.

122. The history of information changes in annexes to the pharmacovigilance system master file can be provided upon request, and in this case, the date of the change and/or update of an annex is included in the changelog with the update of the history of changes in the annex content. It is allowed that regularly updated information in annexes (such as lists of medicinal products, standard operating procedures, or compliance indicators) includes results from controlled systems (e. g., electronic document management systems or authorised authorities' databases). Previous versions of annexes may be managed outside of the master file, provided that the history of changes is maintained and available to the authorised authorities upon request. If the master file has not been requested by an authorised authority or has not been modified for a specified period of time (e. g., if changes to annexes are managed separately from the master file), it is recommended that periodic compliance review of information relevance be carried out. MA holders need to ensure that their obligations regarding the timely provision of the pharmacovigilance system master file are met. Also,

the authorised pharmacovigilance officer shall have access to updated and reliable information about the pharmacovigilance system; therefore, the MA holder shall ensure constant access to the pharmacovigilance system master file, including the information contained in annexes (using the pharmacovigilance system master file itself or through access to the systems used to create the annexes).

123. MA holders shall justify the method chosen and develop documentation control procedures to properly manage the process of maintaining the pharmacovigilance master file. The main principle is that being the basis for audits and inspections, the pharmacovigilance system master file contains a description of the pharmacovigilance system at the current time; still, in some cases, additional assessment of the functioning and focus of the pharmacovigilance system in the previous stages may be required for a correct understanding.

124. When making changes to the pharmacovigilance system master file, it is also necessary to take into account joint pharmacovigilance systems and delegated pharmacovigilance tasks. Adequate change control involves recording the date and context of notifications of changes made by the authorised authorities, authorised pharmacovigilance officers, and third parties.

125. The pharmacovigilance system master file should be stored in such a way as to ensure readability and accessibility.

6. Presentation of the Pharmacovigilance System Master File

126. The authorised pharmacovigilance officer shall have permanent access to the pharmacovigilance system master file. Authorised authorities shall be provided with access to the pharmacovigilance system master file upon request. The information in the pharmacovigilance system master file

must be comprehensive, correct, and reflect the valid pharmacovigilance system at the current time, which means that the information in the master file must be updated and, if necessary, its content must be revised with due account for the experience gained, technical and scientific progress, changes in regulatory standards. A MA holder shall provide the authorised authorities with access to the pharmacovigilance system master file within 7 working days after receiving the relevant request. The MA holders shall provide the authorised authorities with the direct access to the pharmacovigilance system master file at the indicated location of the pharmacovigilance system master file or the place of the authorised pharmacovigilance officer's activity.

7. Format of the Pharmacovigilance System Master File

127. It is allowed that the pharmacovigilance system master file be in electronic form, provided that it is possible to submit a clearly structured hard copy at the authorised authorities' request. In any format, the pharmacovigilance system master file shall be in a readable, complete, and accessible form, allowing for the assessment of all documents and traceability of changes. In some cases, it may be necessary to restrict access to the pharmacovigilance system master file to properly control its content and assign responsibilities for managing it (in the context of change control and archiving). Electronic document tagging and searchable text should be used. Documents such as copies of signed statements or agreements shall be included in the annexes and described in the electronic document index. The documents and data of the master file shall be presented in the following headings and, if they are in a hard copy, shall be presented in the indicated order:

the title page shall contain the number of the pharmacovigilance system master file (if any), the MA holder's name, the authorised pharmacovigilance

officer responsible for the system described, the names of other MA holders (who use this pharmacovigilance system), a list of master files for the MA holders (for medicinal products included in a different pharmacovigilance system), the date of preparation or the last update of the pharmacovigilance system master file.

The headings used in Subsection 4, Section III of these Rules should be used to indicate the main sections of the master file content. The minimum required content of annexes to the master file is set out in paragraph 120 of these Rules; the annexes to the master file may include additional information provided that the requirements for the content of the main sections are met. The annexes include the following information:

data on the authorised pharmacovigilance officer (Annex A):

a list of tasks delegated by the authorised pharmacovigilance officer or a relevant procedural document;

the authorised pharmacovigilance officer’s biography data and documents confirming these data;

additional contact details (if necessary);

organisational structure of the MA holder (Annex B):

lists of contracts and agreements;

safety data sources (Annex C):

lists describing the safety data sources (such as affiliates of the MA holder and third-party contacts);

computerised systems and databases (Annex D);

written processes and procedures (Annex E):

list of procedural documents;

the pharmacovigilance system performance (Annex F):

lists of performance indicators;

current results of evaluating the performance indicators used;

quality system (Annex G):

audit plan;

list of conducted and completed audits;

medicinal products (Annex H):

a list of medicinal products included in this pharmacovigilance system;

comments regarding the MA holders;

records and documentation control (Annex I):

changelog;

history documentation on annex content change containing electronic indexes (according to Annexes A-I and their content), if such change history documentation is not provided in the corresponding annex.

If necessary, the document is accompanied by documentation to confirm the notifications and signatures concerning the pharmacovigilance system master file. In the absence of any of the said annexes, there is no need to provide pages with empty content, however, the submitted annexes shall still be entitled in accordance with the above format. For example, Annex E should not be renamed as Annex D when the annex not related to the computerised systems and databases is used; Annex D should simply be entitled “unused” in the contents to indicate the lack of content.

8. Responsibilities of the Pharmacovigilance System Participants

Marketing Authorisation Holders

128. MA holders shall develop and implement a pharmacovigilance system to monitor and control one or more medicinal products. They are also responsible for creating and maintaining a pharmacovigilance system master file, which describes pharmacovigilance system for authorised medicinal products. The MA holder shall appoint an authorised pharmacovigilance

officer responsible for creating and operating the pharmacovigilance system described in the pharmacovigilance system master file.

129. When applying for marketing authorisation of a medicinal product, the applicant shall have at his/her disposal a description of the pharmacovigilance system that will operate on the Union territory or the territories of individual Member State. During the assessment of the marketing authorisation application, the applicant may be required to submit a copy of the pharmacovigilance system master file for review.

130. The MA holder is responsible for creating a master file in the pharmacovigilance system, which covers the Member States territories and registering the location of the pharmacovigilance system master file with the Member States' authorised authorities when applying for marketing authorisation of a medicinal product. In the pharmacovigilance system master file, it is necessary to describe the current pharmacovigilance system. It is possible to include information about system components that will be deployed in the future and listed as planned rather than deployed or operational.

131. Activities on creating, maintaining, and submitting the pharmacovigilance system master file to the authorised authorities may be entrusted to a third party; however, the marketing authorisation holder is responsible for compliance with the requirements of the Union authorities' acts and the Member States' legislation. Maintaining the pharmacovigilance system master file in operable working condition and access (constant access for audit and inspection) may be delegated; still, the MA holder is permanently responsible for ensuring that this function is performed at a level that meets the requirements of the Union authorities and the Member States' legislation.

132. In case of a change of the authorised pharmacovigilance officer or his/her contacts and change of pharmacovigilance system master file location, a MA holder shall submit to the Member States' authorised authorities an application for making the appropriate changes. MA holders are responsible for updating information about the authorised pharmacovigilance officer and the address of the pharmacovigilance system master file location.

Authorised Authorities of the Member States

133. Authorised authorities of the Member States are responsible for supervision over the pharmacovigilance systems of MA holders. As part of this obligation, the authorised authorities assess the summary information about the pharmacovigilance system included in the marketing authorisation application when applying for marketing authorisation. A complete pharmacovigilance system master file can be requested at any time (e. g., if there are questions about the pharmacovigilance system or the medicinal product's safety profile, or when preparing for an inspection). Information about changes in the brief information on the pharmacovigilance system or the content of the pharmacovigilance system master file is also used during the planning and conduct of the inspection.

134. Authorised authorities exchange information on pharmacovigilance systems, including transferring data to the Member States' inspection programs developed based on the risk analysis. Inspectors from the authorised authorities report non-compliance with mandatory requirements, including the requirements for the pharmacovigilance system master file and the pharmacovigilance system.

9. Availability of the Pharmacovigilance System Master File

135. Pharmacovigilance system master file shall be maintained in operable condition, available for the authorised pharmacovigilance officer. It shall also be available for inspection at all times, regardless of whether a prior notification has been made or not.

136. The MA holder maintains and submits, at the request of the Member State's authorised authority, a copy of the pharmacovigilance system master file. The MA holder submits a copy of the master file within 7 working days after receiving the relevant request. The pharmacovigilance system master file is submitted in a readable form in electronic format or hard copy.

137. If more than one MA holder uses the same pharmacovigilance system master file (in the case of a common pharmacovigilance system), the corresponding pharmacovigilance system master file shall be available for each of them so that each of the MA holders has the opportunity to submit the master file to the Member State's authorised authority within 7 working days after receiving the relevant request.

138. Unless otherwise justified, the pharmacovigilance system master file is not requested during the assessment of new applications for medicinal product authorisation (i. e., before a medicinal product authorisation) but may be requested in special cases, in particular, when introducing a new pharmacovigilance system or when identifying safety concerns of the medicinal product or issues related to compliance with the requirements of the Union authorities' acts and the Member State' legislation in the field of pharmacovigilance.

IV. Inspection of the Pharmacovigilance System

1. General Provisions

139. To confirm the fulfillment of the MA holders' pharmacovigilance obligations, the authorised authorities are obliged to conduct pharmacovigilance inspections of the MA holders or other organisations involved by the MA holders to fulfill the pharmacovigilance obligations. Pharmacovigilance inspections shall be carried out by inspectors appointed by the Member States' authorised authorities, empowered to inspect the premises, get acquainted with materials, documents, and the pharmacovigilance system master file located at the address of the MA holder or other organisations engaged by the MA holder to fulfill the pharmacovigilance obligations. At the request of the Member State's authorised authority, the MA holder is obliged to submit a pharmacovigilance system master file, which will be used as a source of information when conducting inspections.

140. The objectives of pharmacovigilance inspections are as follows:

a) confirmation that a MA holder has the personnel, systems, and premises, tools, and equipment necessary to fulfill the pharmacovigilance obligations;

b) identification, assessment, and registration of inconsistencies that may pose a risk to public health and informing the inspected party about this;

c) using the results of inspections as the basis for the MA holder's mandatory actions (if necessary).

141. The authorised authority of a Member State is entitled to conduct pharmacovigilance inspections before authorisation to verify the compliance of a MA holder's current pharmacovigilance system with the requirements of the legislation of the Member State and these Rules. The authorised

authorities interact to exchange information regarding the planned inspections and the results of inspections that have already been carried out. Concerning the holders of marketing authorisation certificates for products authorised according to the decentralised procedure or the mutual recognition procedure, the authorised authority of the reference state is responsible for assessing the compliance of the MA holder's pharmacovigilance system with the requirements of these Rules at the authorisation stage, including the conduct of a pre-authorisation inspection of the MA holder's pharmacovigilance system according to the criteria for the feasibility of conducting the pre-authorisation inspection in accordance with paragraphs 157–159 of these Rules.

142. Pharmacovigilance inspection programs include routine inspections according to a risk-based approach and unscheduled inspections carried out to assess suspected non-conformities or potential risks that may affect the performance of the pharmacovigilance function in relation to a particular medicinal product.

143. The authorised authorities organize inspections of MA holders, ensuring interaction at the stage of planning and conducting inspections to minimize duplication of work performed and optimize the use of available resources.

144. The inspection results shall be submitted to the inspected party, which is allowed to provide its comments in case of non-compliance with the requirements of the Member State's legislation and these Rules. The MA holder shall promptly eliminate the identified discrepancy by developing and implementing a corrective and preventive action plan.

145. Where the inspection reveals that a MA holder does not comply with the pharmacovigilance obligations, the authorised authority shall inform other Member States' authorised authorities about the violation detected. If

necessary, the Member State’s authorised authority shall ensure that effective, proportionate, and deterrent measures are applied to the MA holder. Information on the conduct and results of pharmacovigilance inspections, as well as on subsequent control and assessment of consequences, is posted by the Member States on the official websites of the relevant authorised authorities in the Internet network.

2. Types of Inspections

Inspection of the Pharmacovigilance System as a Whole and for Individual Medicinal Products

146. Pharmacovigilance system inspections aim to assess and analyze existing procedures, systems, personnel, premises, and equipment and determine their compliance with the pharmacovigilance obligations established by the legislation of the Member States and these Rules. In this analysis, specific examples of medicinal products can be used to demonstrate and verify the pharmacovigilance system operation.

147. Inspections aimed at assessing the performing pharmacovigilance functions for a specific medicinal product include assessing and analyzing activities and documentation related to the specified medicinal product. Certain sections of the overall pharmacovigilance system used in performing functions for the inspected medicinal product may also be subject to assessment as part of a pharmacovigilance inspection.

Scheduled and Unscheduled Inspections of Pharmacovigilance Systems

148. Scheduled pharmacovigilance system inspections are carried out in accordance with a previously drawn-up inspection plan. To optimize the planning of measures to control the pharmacovigilance system’s functioning,

the approach based on assessing the potential risks of non-compliance with the relevant obligations is applied. Scheduled inspections are systemic inspections where one or more specific medicinal products can be selected as samples for checking the functioning of the pharmacovigilance system and obtaining practical evidence of its effective functioning and compliance with the requirements of the Union authorities' acts and the Member State's legislation. A routine inspection program could, for example, include an assessment of the state of the system for specific problems identified by experts.

149. Unscheduled pharmacovigilance system inspections are carried out if an initiating factor (systemic problem) is detected; in contrast, an inspection is considered the most optimal way to study and evaluate the problem identified. Unscheduled inspections aim to assess specific pharmacovigilance processes or study the identified problem(s) and its impact on a particular medicinal product. In some instances, depending on the identified initiating problem, inspections can be carried out with a full assessment of the pharmacovigilance system. Unscheduled inspections are carried out in case one or more of the initiating factors specified in paragraphs 150–155 of these Rules have been detected.

150. The following factors in terms of the benefit-risk ratio of the medicinal product are the basis for performing an unscheduled inspection:

changing the risk–benefit ratio if it seems necessary to further assess the system by conducting an inspection;

delay in implementation, or improper implementation of the procedure for identifying risk or informing about a change in the risk–benefit ratio, or failure to comply with this procedure;

submitting information on the pharmacovigilance issues to the media without prior or simultaneous notification of authorised authorities;

non-compliance with the requirements of the Union authorities' acts and the Member State's legislation or obligations to ensure the medicinal product safety, detected while monitoring the pharmacovigilance activities by authorised authorities;

suspension of circulation or withdrawal from the market of a medicinal product without prior notification to the Member States' authorised authorities.

151. In terms of obligations to provide information (urgent and periodic ones), the following factors are the grounds for performing an unscheduled inspection:

delay or failure to fulfill obligations to provide information on safety concerns in accordance with the requirements of the acts of the Union authorities' acts and the Member State's legislation;

low quality (including inaccuracy, non-traceability, lack of integrity) or incompleteness of the information provided;

inconsistency between the information provided and other sources of information;

152. The following factors in terms of requests from authorised bodies are the grounds for performing an unscheduled inspection:

refusal to submit the requested information within the time frame specified by the authorised authorities;

poor quality of the data submitted or their inadequate submission upon requests from the authorised authorities for the information provision.

153. In terms of fulfilling the established obligations, the following factors are the grounds for performing an unscheduled inspection:

concern (reasoned opinion regarding the lack of organisational structure, resource base, or the pharmacovigilance quality assurance system

at the disposal of a MA holder) about the status or fulfillment of obligations under the risk management plan;

delay or non-fulfillment of specific obligations related to product safety monitoring identified during the procedure for examining the marketing authorisation application;

poor quality of reports submitted in response to a request for compliance with obligations.

154. The following factors related to prior inspections are grounds for performing an unscheduled inspection:

delay in implementation or inappropriate implementation of corrective and preventive actions.

information obtained during other inspections for compliance with the requirements of good pharmaceutical practices on non-compliance with the requirements of the Union authorities' acts and the Member State's legislation, taking into account the obligations established by the Member State's authorised authority in the field of medicinal products circulation;

verification of information received from other Member States' authorised authorities for revealing inconsistencies in the pharmacovigilance system.

155. In addition to the factors specified in paragraphs 150–154 of these Rules, the following factors are also the grounds for performing an unscheduled inspection:

problems identified when reviewing the pharmacovigilance system master file;

other information or incoming complaints (claims) indicating that a MA holder does not have a pharmacovigilance system or pharmacovigilance quality assurance system.

Pre-authorisation Inspections

156. Pre-authorisation inspections of pharmacovigilance system are carried out before the issuance of marketing authorisation to the applicant. The purpose of such inspections is to examine a functioning or planned pharmacovigilance system in accordance with the applicant's description of the system. Pre-authorisation inspections of the pharmacovigilance system are not mandatory but they may be necessary under certain circumstances. The principles of requesting for a pre-authorisation inspection shall be justified by the authorised authority (expert organisation) subject to the criteria for appointing pre-authorisation inspections specified in paragraph 157 of these Rules, and shall not be the reason for unreasonable inspections that may delay the marketing authorisation issuance.

157. The following factors should be taken into account when considering the feasibility and reasonableness of performing pre-authorisation inspections:

the applicant has not previously worked with the existing pharmacovigilance system in the Member States territories or is at the stage of creating a new pharmacovigilance system;

information received on the MA holder's complaints about fulfilling the pharmacovigilance system requirements (e. g., the history of previous inspections or non-compliance notification/information from other Member States' authorised authorities). If the MA holder has a history of serious and/or persistent non-compliance of the pharmacovigilance system with the current requirements, then the pre-authorisation inspection of the pharmacovigilance system may be one of the mechanisms to confirm that the system has been appropriately corrected or improved;

the existence of safety concerns related to particular medicinal products where it may be deemed necessary to assess the marketing authorisation holder’s ability to:

implement risk minimisation measures associated with a specific medicinal product;

properly meet special requirements to ensure the safety of the use of medicinal products that may be established;

properly implement procedures of routine pharmacovigilance activities in relation to a medicinal product, which safety profile causes concern.

Decision-making on the implementation of a pre-authorisation inspection includes a risk assessment with a comprehensive assessment of issues related to certain medicinal products and the system.

158. Should the pre-authorisation inspection of the pharmacovigilance system raise any concerns about the ability of a MA holder to comply with the requirements for the pharmacovigilance system established by the legislation of the Member State and these Rules, the Member State’s authorised authority may take the following measures:

a) refusal to issue marketing authorisation, non-confirmation of authorisation (renewal), or other approval procedures;

b) performing a re-inspection before the issuance of marketing authorisation to confirm the elimination of critical inconsistencies and the implementation of recommendations;

c) issuance of marketing authorisation with a recommendation to inspect the pharmacovigilance system at an early post-authorisation stage. The limitation of the time-frame for performing a re-inspection, being included in the scheduled inspections plan, is determined based on an assessment of inconsistencies and their impact on the fulfillment of the MA holder’s pharmacovigilance obligations;

d) determining the conditions for ensuring the safety of a medicinal product when issuing marketing authorisation.

Post-authorisation Inspections

159. Post-authorisation pharmacovigilance system inspections are carried out after getting marketing authorisation and are designed to assess the fulfillment of the MA holder's pharmacovigilance obligations. Post-authorisation inspections can be of any type in accordance with paragraphs 146–149 of these Rules.

Announced and Unannounced Inspections

160. Most pharmacovigilance system inspections are announced, which entails notifying the inspected party to ensure that appropriate persons are present in the place of inspection during the inspection. In some cases, it is advisable to conduct unannounced inspections or notify the inspected party on the eve of the inspection (e. g., if a preliminary announcement could jeopardize the inspection objectives or if the inspection is carried out urgently on a tight schedule for safety reasons).

Repeat Inspections

161. Re-inspections can be carried out regularly as part of the pharmacovigilance system inspection plan. Risk factors need to be assessed to prioritize re-inspections. Re-inspection at an early stage can be carried out if a significant number of inconsistencies are identified, and confirmation of the proper implementation of actions and measures aimed at correcting the comments is required, and an assessment of the continued fulfillment of obligations and compliance with the requirements for the pharmacovigilance

system, including the evaluation of changes in the pharmacovigilance system. An early re-inspection is advisable shortly after the previous inspection if there is information that the inspected party has not followed appropriate corrective and preventive actions as directed by an earlier inspection.

Remote Inspections

162. Inspectors carry out remote pharmacovigilance system inspections without visiting a MA holder or the organisation to which the pharmacovigilance functions are delegated. These inspections are carried out using the Internet network or telephone communication. This type of inspection can also be used in case of logistical difficulties (e. g., in the case of a pandemic or transport restrictions) when conducting an on-site inspection under exceptional circumstances and, if it is possible, to arrange interviews of relevant personnel and an assessment of documentation, including safety databases, primary documentation, and a pharmacovigilance system master file via remote access. The decision to conduct a remote inspection at the inspectors' discretion is subject to agreement with the Member State's authorised authority issuing the inspection order. Logistic aspects of remote inspection should be coordinated with the MA holder. If, during the remote inspection, issues are identified requiring an on-site assessment of the pharmacovigilance system, a decision is made to conduct an on-site inspection.

3. Inspection Planning

163. The planning of pharmacovigilance system inspections shall be based on a systematic risk-based approach to optimize the use of resources in the ongoing monitoring activities and ensure a high level of public health

protection. A risk-based approach to inspection planning determines the frequency, focus, and scope of inspections.

164. Pharmacovigilance system inspection plans are drawn up by the Member States' authorised authorities taking into account the following:

a) factors associated with inspection:

history of identifying inconsistencies from previous pharmacovigilance inspections or other types of inspections (in accordance with Good Pharmaceutical Practice);

the date of re-inspection recommended by inspectors or experts as a result of a previous inspection;

b) factors associated with medicinal products:

availability of a valid marketing authorisation for the medicinal product for which additional pharmacovigilance activities or additional risk minimisation measures are prescribed;

authorisation of a medicinal product for which post-authorisation safety studies or additional monitoring are prescribed;

authorisation and delivery of a medicinal product with a large sales volume, i. e., with a potentially significant impact on large patient populations;

authorisation of a medicinal product that has no alternative on a Member State's market;

c) factors associated with the MA holder:

the MA holder has never undergone a pharmacovigilance inspection;

the MA holder has a significant number of medicinal products in circulation in the markets of the Member States;

the MA holder did not previously have any marketing authorisation in the territories of the Member States;

availability of negative information on the fulfillment of mandatory requirements and/or on emerging safety issues related to medicinal products that was received from the Member States' authorised authorities and other countries carrying out pharmacovigilance, as well as from authorised authorities in other areas of regulation of the medicinal products circulation (i. e., in relevant Good Pharmaceutical Practices);

changes emerging in the organisational structure of a MA holder, such as mergers and acquisitions;

d) factors associated with a pharmacovigilance system:

engaging a subcontractor by the MA holder to carry out pharmacovigilance activities (in terms of the authorised pharmacovigilance officer's functions, safety data submission, etc.) and/or several organisations involved in carrying out pharmacovigilance activities;

replacing the authorised pharmacovigilance officer since the last inspection;

changes in the safety database(s) for medicinal products, which may include changes in the database itself or related databases, the status of database validation, as well as information on transmitted or transferred data;

changes in contractual relationships with pharmacovigilance service providers or pharmacovigilance sites;

delegating or transferring the management of the pharmacovigilance system master file.

165. The Member States' authorised authorities ensure the placement of the inspection plan of MA holders on the official web portal of the Member States' authorised authorities for the coming calendar year at least 45 calendar days before the period of implementation of the inspection plan.

166. Authorised authorities of the Member States have the right to request the required information from MA holders to plan inspections on a risk-based assessment approach if it is not available at the time of planning.

4. Inspected Sites

167. Any party that in whole or in part carries out pharmacovigilance activities on behalf of a MA holder or jointly may be inspected to confirm that the MA holder can adequately fulfill the obligations and comply with mandatory pharmacovigilance requirements. Inspected sites may be located on the Member States' territories or in the territories of third countries. Sites in the territories of third countries may be inspected if the main pharmacovigilance center, the main database creation center and/or pharmacovigilance activities are located (performed) in the territories of third countries. The type and number of inspected sites shall be selected so that to ensure that the inspection's key objectives are met.

5. Inspection Scope

168. Inspection scope depends on inspection objectives, the coverage of previous inspections by the Member States' authorised authorities, and inspection type. When planning the inspection scope, it is necessary to take into account:

a) Information provided in the pharmacovigilance system master file;

b) information on the functioning of the pharmacovigilance system (e. g., data on the pharmacovigilance system's compliance available to the Member State's authorised authority);

c) specific factors for initiating an inspection in accordance with paragraphs 150–155 of these Rules.

Inspection Scope During Planned Pharmacovigilance Inspections

169. Scheduled inspections of the pharmacovigilance system check the compliance with the requirements of the Union authorities' acts and the Member State's legislation in the field of pharmacovigilance. Depending on the type of inspection, the inspecting shall include an assessment of the following system elements:

a) procedures for handling individual case safety reports for a medicinal product:

collection and exchange of reports received from all sources, from sites and organisations within the pharmacovigilance system, including from those organisations that, on a contractual basis, fulfill a MA holder's pharmacovigilance obligations as well as from other organisational units not related to the pharmacovigilance system;

evaluation of reports, including mechanisms for receiving and registration procedure, assessment of reporters, the terminology used, assessment of seriousness, foreseeability, and causality;

recording the results of subsequent data collection and outcomes (e. g., the outcome in cases of fetal drug exposure during pregnancy and medical confirmation of patient reports);

compliance with the requirements of the Union authorities' acts and the Member States's legislation on the submission of various types of individual case safety reports for a medicinal product to the relevant Member States' authorised authorities;

documentation and archiving of individual case safety reports;

b) periodic safety update reports (if applicable):

completeness and reliability of the data included; the validity of decisions related to the data that are not included;

correct submission and assessment of safety information, identification of changes to the safety profile, submission of results of relevant analyses and measures;

registration and presentation of information in a periodic safety update report in accordance with the established requirements;

timeliness of report submission;

c) continuous assessment of the safety profile:

use of all information sources for signal detection;

correct application of information analysis methodology;

consistency of investigation and follow-up procedures (e. g., implementation of recommendations after data analysis);

implementation of the risk management plan or other obligations;

timely identification and submission of complete and accurate data to the Member States' authorised authorities, particularly in response to specific data requests;

inclusion of approved changes in used safety information reports and medicinal product information, including internal communications and addresses to healthcare professionals and patients;

d) interventional (if necessary) and non-interventional clinical trials:

reporting suspected unexpected serious adverse reactions in accordance with the requirements of these Rules, the Good Clinical Practice principles of the Eurasian Economic Union, approved by Decision of the Council of the Eurasian Economic Commission No. 79 dated November 3, 2016, and the legislation of the Member States;

obtaining, registering, and evaluating cases of adverse reactions identified in the course of interventional and non-interventional clinical trials;

presentation of study results and relevant safety information on medicinal products in the form of reports in accordance with the

requirements of these Rules, the Good Clinical Practice principles of the Eurasian Economic Union, and the legislation of the Member States;

appropriate selection of safety references, keeping up to date information in Investigator’s brochures or patient safety information;

inclusion of study data in the current safety assessment of a medicinal product;

e) pharmacovigilance system procedures:

the authorised pharmacovigilance officer’s roles and responsibilities, for example, access to the pharmacovigilance quality system, the pharmacovigilance system master file, performance indicators, and pharmacovigilance system indicators, audit and inspection reports related to the pharmacovigilance system, and their ability to take action to improve compliance of the pharmacovigilance system with the requirements of the Union authorities’ acts and the Member States’s legislation;

roles and responsibilities of a MA holder concerning the pharmacovigilance system;

accuracy, completeness, and maintenance of the current level of information in the pharmacovigilance system master file;

quality and compliance with the level of training, qualifications, and experience of the personnel;

Coverage and compliance of the quality system with respect to the pharmacovigilance system, including the implementation of quality control and quality assurance processes.

suitability of the computerised systems used to perform specific functions;

agreements with all parties involved, appropriately reflecting the responsibilities and activities for performing pharmacovigilance and proper implementation;

f) conformity with the authorisation conditions and compliance of the implemented risk minimisation measures with the established requirements (if necessary).

Inspection Scope During Unscheduled Pharmacovigilance Inspections

170. The scope of an unscheduled inspection depends on the reasons for its initiation. The evaluated aspects of the system may include those specified in paragraph 169 of these Rules, as well as the following:

a) involvement and awareness of the authorised pharmacovigilance officer on issues related to a specific medicinal product;

b) detailed study of processes, decision-making procedures, implementation of information, and implementation of measures related to a specific factor in initiating an inspection and/or a medicinal product.

Inspection Scope During Repeated Pharmacovigilance Inspections

171. When determining the scope of work for a re-inspection, the following aspects should be considered:

a) analysis of the state of the system and/or corrective and preventive action plan developed based on the previous pharmacovigilance inspection results;

b) analysis of significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection (e. g., changes in the pharmacovigilance database, merger or acquisition of a company, significant changes in contractual activities, replacement of the authorised pharmacovigilance officer);

c) analysis of the processes and/or issues concerning a specific medicinal product identified as a result of assessing the information provided by a MA holder or not included in the scope of the previous inspection:

The results of previous inspections determine the scope of a re-inspection; it can be expanded, considering several factors (e. g., time from the date of the previous inspection, the scope of the previous inspection).

6. Inspection Process

172. Pharmacovigilance inspections need to be planned, coordinated, carried out, reported, followed up, and documented following the inspection procedures carried out in the Member States territories. The improvement and harmonisation of inspections will be facilitated by agreed processes and procedures, joint inspections, exchange of experience, and training of the inspectorates of the Member States' authorised authorities.

173. Pharmacovigilance systems procedures shall include the following main processes (where necessary, new procedures may be developed):

a) exchange of information;

b) inspection planning;

c) pre-authorisation inspections;

d) coordination of pharmacovigilance system inspections in the Member States;

e) coordination of inspections carried out in countries that are not members of the Union (including inspections of contractors);

f) preparation of pharmacovigilance system inspections;

g) conduct of pharmacovigilance system inspections;

h) reporting on pharmacovigilance system inspections and follow-ups;

i) informing and prioritizing pharmacovigilance inspections and the results obtained;

j) keeping records and archiving of documents received after pharmacovigilance system inspections;

k) unannounced inspections;

l) sanctions and regulatory or enforcement measures in case of serious non-compliance with the requirements of the legislation of the Member States and these Rules;

m) instructions for the training of inspectors performing pharmacovigilance system inspections and the experience exchange.

7. Monitoring the Implementation of Inspection Remarks

174. If non-compliance with pharmacovigilance obligations is identified during the inspection, follow-up is required until the full implementation of the corrective and preventive action plan. The following control methods should be considered:

a) analysis of the corrective and preventive measures of the MA holder:

b) analysis of periodic reports on the work progress according to the corrective and preventive action plan (if necessary);

c) re-inspection to assess the proper implementation of the corrective and preventive action plan;

d) A request for submission of previously unreported data, changes (e. g., information about a medicinal product), impact analysis (e. g., the result of analysis of data that were not previously included in the analysis when performing a signal detection procedure);

e) a request to properly implement the information sharing, including introducing changes to the information provided within marketing activities and/or advertising information;

f) a request for a meeting with a MA holder to discuss the identified deficiencies (inconsistencies) and their impact on the corrective and preventive action plan;

g) transmission of the inspection results to other authorised authorities of the Member States;

h) other actions related to a medicinal product, depending on the impact of deficiencies (inconsistencies) and the results of subsequent actions (this may include reviews or actions related to the issuance of marketing authorisation certificates or clinical study approval).

8. Actions and Sanctions of the Member States' Authorised Authorities

175. The authorised authorities ensure control over the fulfillment of MA holders' pharmacovigilance obligations in accordance with the legislation of the Member States and these Rules. If non-compliance with requirements or non-fulfillment of pharmacovigilance obligations, the actions to be taken shall be determined on a case-by-case basis. The choice of necessary actions depends on the potential negative impact of non-conformity (non-compliance) on public health (health of population) but any case of non-conformity (non-compliance) may be taken into account when applying enforcement measures. Where necessary, the authorised authority shall ensure that effective, proportionate and deterrent measures are applied to the MA holder.

176. In accordance with these Rules and the rules established by the legislation of the Member States (where necessary), in case the MA holder fails to comply with the pharmacovigilance obligations, the following measures may be taken:

a) training and assistance: authorised authorities of the Member States communicate with representatives of MA holders (e. g., at a meeting) to

summarize the identified inconsistencies, clarify the established requirements and expectations of the Member State's authorised authority and consider corrective and preventive actions proposed by the MA holder;

b) submission of information to other authorised authorities of the Member States within the framework of confidentiality agreements;

c) inspection of MA holders who do not comply with the obligations or do not fulfill the requirements can be carried out to determine the degree of non-compliance (failure to fulfil) with the Union authorities' acts and the Member States' legislation and subsequently to confirm their compliance (fulfillment);

d) sending a warning letter, statement of non-compliance (failure to fulfill) with the pharmacovigilance obligations, or notification of a violation of pharmacovigilance obligations issued by the Member State's authorised authority with an indication of the regulatory legal act that was violated to remind the MA holders of their pharmacovigilance obligations or the measures that they shall take, as well as on the deadlines set for eliminating the inconsistencies or violations;

e) consideration by the Member States' authorised authorities of the issue of publishing a list of MA holders who seriously or permanently violate the requirements of the Union authorities' acts and the Member States' legislation;

f) actions regarding the marketing authorisation certificate or marketing authorisation application for a medicinal product, for example:

urgent introduction of restrictions related to the safety profile of a medicinal product;

introduction of changes to the marketing authorisation application for a medicinal product;

suspension or cancellation of the marketing authorisation of a medicinal product;

suspension of consideration of new applications for obtaining marketing authorisation until the corrective and preventive actions are implemented;

appointment of pre-authorisation inspections of the pharmacovigilance system;

g) withdrawal of a medicinal product from the market (e. g., if important, safety precautions are not included in the product information);

h) actions related to marketing or advertising information;

i) making changes to protocols or suspension of clinical trials in case of identification of changes in the safety profile of a specific medicinal product;

j) administrative fines in accordance with the legislation of the Member States.

9. Inspectors' Qualifications and Training

177. Inspectors who conduct pharmacovigilance system inspections shall be specialists from the Member States' authorised authorities or persons appointed in accordance with the requirements of the legislation of the Member State and shall also comply with the provisions of the quality manual for the inspectorate of the Member State's authorised authority. Inspectors should be appointed subject to their experience and requirements as determined by the competent authority. Inspectors shall be trained to the extent necessary to ensure that they are competent in the areas required to prepare and conduct inspections and to prepare an inspection report. They shall also be trained in the processes and pharmacovigilance requirements in such a way as to be able to assess various aspects of the pharmacovigilance system in the absence of relevant experience.

10. Quality Management in the Pharmacovigilance Inspection Process

178. The quality of the pharmacovigilance system inspection process is regulated by authorised authorities, includes among the issues covered by the pharmacovigilance quality system of the Member State's authorised authority and is subject to audit. The Member States' authorised authorities formulate harmonised inspection procedures to ensure the quality, consistency, and mutual recognition of the results of the pharmacovigilance system inspection of MA holders.

11. Cooperation within the Union Information Sharing

179. The authorised authorities shall cooperate to facilitate the information exchange concerning pharmacovigilance system inspections, in particular:

a) information on inspections that are planned and carried out to eliminate unnecessary repetitions and duplication of work in the Union and optimize the use of inspection resources;

b) information on the inspection scope in order to plan the next inspections;

c) information on the inspection results, particularly when the result identifies the fact that the MA holder has not complied with the requirements of the legislation of the Member States and these Rules.

180. The Member States' authorised authorities exchange information on critical and significant identified deficiencies and a summary of corrective and preventive actions and their further control.

12. Role of the Member States' Authorised Authorities

181. The authorised authorities shall ensure the establishment of a legal and organisational basis for performing the functions of inspecting the pharmacovigilance systems of MA holders, including determining the inspectors' rights concerning the pharmacovigilance activities inspection and the pharmacovigilance data assessment.

182. The Member States shall allocate adequate resources and qualified inspectors to ensure effective implementation of the procedure for assessing the compliance of MA holders with pharmacovigilance obligations in accordance with the requirements of the Member States and these Rules. If necessary, subject matter experts for pharmacovigilance activities can be involved in the conduct of inspections. The authorised authorities may, where necessary, send a request for assistance in inspecting another authorised authority with the provision of appropriate access to the inspection site and the evaluated data of the pharmacovigilance system.

183. The authorised authorities of the Member States shall ensure the planning and conduct of pharmacovigilance system inspections of MA holders in accordance with Subsection 2, Section IV of these Rules.

184. When developing the inspection plan, the authorised authority of the Member State asks authorised authorities of other Member States regarding the inspection status and plans for the inspection of MA holders that are supposed to be included in the inspection plan and ensures planning taking into account plans for the inspection of other authorised authorities of the Member State to minimize unreasonable duplication of work performed and optimizing the use of available resources.

185. Should the Member State's authorised authority plan to inspect the MA holder who was inspected by another authorised authority of the Member

State, the exchange of information on the scope and results of the inspection performed shall be ensured to account for the available data when planning, determining the scope and the time of the inspection.

186. A single information resource should be formed, containing the inspection results of MA holders' pharmacovigilance systems, and the Member States' authorised authorities shall have access thereto.

13. Role of MA Holders

187. Holders of marketing authorisation certificates for medicinal products authorised in the Member States territories are subject to pharmacovigilance system inspections. MA holders shall:

a) always be ready for inspection, as inspections can be unannounced;

b) maintain the pharmacovigilance system master file and submit it at the inspectors' request within 7 working days after receiving the corresponding request;

c)ensure that previous inspection consent is obtained for the conduct of an inspection from sites selected for inspection, which may include organisations performing pharmacovigilance activities by agreement with a MA holder;

d)provide inspectors with any information and/or documentation necessary to prepare for the inspection, on time or during the inspection;

e) ensure that appropriate personnel involved in pharmacovigilance activities are present during the inspection and provide clarification on emerging issues;

f) ensure the proper and timely implementation of corrective and preventive action plans to eliminate deficiencies (inconsistencies) identified during the inspection with prioritisation of critical and significant deficiencies (inconsistencies).

14. Inspection Fees

188. Inspection fees are levied in accordance with the legislation of the Member States.

V. Pharmacovigilance System Audit

1. Pharmacovigilance System Audit and Its Objectives

189. The purpose of the pharmacovigilance system audit is to confirm the compliance and effectiveness of the pharmacovigilance system's implementation and functioning by analyzing and assessing objective facts, including the pharmacovigilance quality system.

190. An audit is a systematic, orderly, independent, and documented process of obtaining and objectively assessing the facts characterizing the pharmacovigilance system's operation to determine the degree of fulfillment of audit criteria improved the risk management, control and management of processes. Audit facts consist of records, documentary evidence, or other relevant information to audit criteria and verifiable. The audit criteria reflect the standards of activity and control over it against which the auditee and its performance are assessed. Concerning the pharmacovigilance system, the audit criteria shall reflect the pharmacovigilance system's requirements, including the quality system of the pharmacovigilance procedures performed, which are determined by the requirements of the legislation of the Member States and these Rules.

2. Risk-based Approach to Pharmacovigilance Audits

191. A risk-based approach is an approach that uses methods to define the area of risk. Risk is understood as the probability of an event occurring that will affect the achievement of the set objectives, considering the

seriousness of its consequences and/or the likelihood of not being detected by other methods. The risk-based approach to the audit focuses on the highest risk areas to the organisation's pharmacovigilance system, including the pharmacovigilance quality system. The risk of harm to public health is of paramount importance. The risk is assessed at the following stages:

strategic audit planning, which results in an audit strategy (long-term approach) that must be approved by top management;

tactical audit planning that results in an audit program, setting audit objectives, and audit scope;

operational audit planning that results in an audit plan for individual audit tasks, prioritizing audit tasks based on risk assessment, using risk-based sampling and testing techniques, reporting audit results according to the relative level of risk, and making audit instructions.

The risk assessment shall be documented for strategic, tactical, and operational planning of the auditing activities of the organisation's pharmacovigilance system.

Strategic Audit Planning

192. The audit strategy is a top-level determination of the planning of audit activities scheduled for a period exceeding one year (usually for 2 to 5 years, unless otherwise justified by the MA holder). The audit strategy includes a list of audits that may be sufficient. The audit strategy is used to determine the audit scope, the topic of the audit, and the methods and assumptions (including, for example, risk assessment) on which the audit program is based.

193. The audit strategy shall cover the organisation of process management, risk management, and internal controls for all pharmacovigilance system components, including the following:

a) all pharmacovigilance system processes and tasks;

b) quality system in pharmacovigilance activities;

c) interaction and liaisons with other departments (if necessary);

d) pharmacovigilance activities carried out by subordinate organisations or delegated to another organisation (e. g., regional sites providing information, branches of a MA holder, third parties such as contractors and other MA holders).

194. Risk factors to be considered when performing a risk assessment procedure include, but are not limited to:

a) changes related to pharmacovigilance issues in the Member States' legislation or in these Rules;

b) major reorganisation or other transformations of the pharmacovigilance system, mergers, acquisitions;

c) changes in key management functions;

d) the risk of a shortage of properly trained and experienced pharmacovigilance personnel (e. g., due to significant personnel turnover, deficiencies in training processes, increased workload);

e) significant changes in the pharmacovigilance system since the previous audit (e. g., introducing a new database on pharmacovigilance activities or a significant update of the existing database, changes in processes and activities subject to the new requirements of the Member States' legislation);

f) the first medicinal product on the market (for MA holders);

g) additional risk minimisation measures introduced for the medicinal product on the market or other circulation conditions related to the product safety profile (e. g., the establishment of additional monitoring);

h) the degree of process criticality, in particular:

in terms of the Member States' authorised authorities – how critical the area or process is for the proper functioning of the Member States' pharmacovigilance system and the overall objectives of the healthcare system;

in terms of MA holders – how critical the area or process is for the proper functioning of pharmacovigilance system. When deciding to audit a branch or a third party, the MA holder shall take into account the nature and criticality of the pharmacovigilance activities currently carried out by an affiliate or a third party on behalf of the MA holder besides accounting for other said factors;

i) the results of previous audits (whether this area or process has ever been audited, the previous audit results). If there are results from previous audits, they are taken into account when determining the time-frame and scope of subsequent audits;

j) identified procedural deficiencies (inconsistencies) in particular areas of activity or processes;

k) other information on the fulfillment of obligations in accordance with the requirements of pharmacovigilance legislation:

for the Member States' authorised authorities – information on compliance with the requirements of pharmacovigilance legislation according to the assessment or audit by external organisations.

for MA holders – information on compliance with requirements according to inspection reports, assessments or audits performed by external organisations, complaints or grievances in terms of pharmacovigilance obligations;

l) other organisational changes that may negatively affect the area of activity or process (e. g., if there is a change in an assistance function such as information and technical support).

Tactical Audit Planning

195. An audit plan is a list of audits consisting of one or more audits scheduled for a specific period (for example, for 1 year). The audit plan shall be prepared in accordance with the long-term audit strategy. The audit plan shall be approved by top management with overall responsibility for the operational and management structure.

196. The audit plan is based on a proper risk assessment and shall focus on assessing the following:

a) pharmacovigilance quality system;

b) critical processes in the pharmacovigilance system;

c) key ways to control the pharmacovigilance system functioning based on pharmacovigilance activities;

d) high-risk areas after implementation of procedures for controlling and taking risk minimisation measures.

197. The risk-based audit plan shall also account for the results of previous audits in terms of insufficient coverage of activity areas, high-risk areas, and a direct designation of management and/or persons responsible for the pharmacovigilance system.

198. The audit planning documentation shall include a summary of each audit plan to be conducted, including the audit scope and objectives. The justification for the timing, frequency, and scope of individual audits that are part of the audit plan shall be based on a documented risk assessment. Risk-based audits of the pharmacovigilance system shall be carried out regularly in compliance with the requirements the Union authorities' acts and the Member States' legislation. Reasonable changes to the audit program shall be properly documented.

Audit Planning and Reporting at the Operational Level

199. An organisation shall implement procedures for planning and conducting individual audits adopted in the form of written documents. The time frame for all measures required to complete an individual audit shall be established in the relevant audit procedures. The organisation shall ensure that audits are conducted following these procedures in accordance with this section.

200. Individual pharmacovigilance system audits shall be carried out under the approved risk-based audit program in accordance with paragraphs 196 and 197 of these Rules. When planning individual audits, the auditor identifies and assesses the risks associated with the area under consideration using the most appropriate sampling and testing techniques. The audit method is appropriately documented in the audit plan.

201. Auditors' findings are documented in the auditor's report and timely reported to management. The audit process shall include mechanisms for communicating findings to the audited party, obtaining feedback and presenting audit reports to management and stakeholders, including those responsible for the pharmacovigilance system, in accordance with the requirements of the Union authorities' acts, the Member States' legislation, and guidelines for the pharmacovigilance system auditing. Audit results shall be reported according to the relative level of risk and classified to indicate their criticality to risks affecting the pharmacovigilance system, processes, and process components.

202. The classification system shall be defined in the pharmacovigilance quality system description and shall account for the following thresholds, which shall be used in further reporting:

A critical deficiency is a fundamental inconsistency in one or several processes or procedures of the pharmacovigilance system, which negatively affects the entire pharmacovigilance system and/or the rights, safety, and well-being of patients, and/or poses a potential threat to public health and/or a serious violation of the requirements of the Union authorities' acts, the Member States' legislation;

a significant deficiency is an important inconsistency of one or several processes or procedures of the pharmacovigilance system or a fundamental deficiency of any part of one or several processes or pharmacovigilance procedures, which adversely affects the entire process and/or can potentially affect the patients' rights, safety and well-being, and/or may pose a potential threat to public health and/or creates a violation of the requirements of the Union authorities' acts and the Member States' legislation, which is not considered serious;

an insignificant deficiency is an inconsistency of any component of one or more processes or procedures of the pharmacovigilance system, which, as expected, cannot adversely affect the entire pharmacovigilance system or process and/or the patients' rights, safety, and well-being.

It is necessary to immediately inform the audited entity's management and the MA holder's top management on issues that need to be addressed urgently.

3. Actions Based on the Audit Results and the Follow-Up Control of Audits

203. Immediate actions, prompt actions, actions within a reasonable time frame, as well as issues on which an urgent decision or urgent information is required, specified in this section are intended to be performed within a time frame that is appropriate, relevant, and consistent with the

relative risk to the pharmacovigilance system. It is necessary to establish priorities for corrective and preventive actions to eliminate the identified critical and significant deficiencies (inconsistencies). The exact time frame for actions associated with an identified critical deficiency (inconsistency) may vary depending on the nature of the findings and the planned action.

204. The management of the audited organisation ensures that the organisation has a mechanism to resolve issues related to the pharmacovigilance system audit results properly. The set of measures shall include an analysis of the initial cause of the identified deficiency, the impact of the specified audit results, and the preparation of a corrective and preventive action plan.

205. Top management of the organisation and those charged with governance shall ensure that all necessary and effective measures are taken to correct deficiencies detected during the audit. The implementation of the agreed actions shall be systematically monitored. Information on the progress of implementing corrective and preventive actions shall be periodically brought to top management's attention according to the planned actions. The facts confirming the completion of the complex of corrective and preventive actions shall be properly documented. The audit program shall include the potential for surveillance audits to be performed as needed to confirm that agreed actions have been completed.

4. Quality and Documentation System

Audit Quality Management. Independence and objectivity of the audit and auditors' work.

206. The auditing organisation shall provide for specific responsibilities in terms of pharmacovigilance audit activities. The activities for performing the pharmacovigilance system audits shall be independent. The management

of the auditing organisation shall ensure and document the auditors' independence and objectivity.

207. Auditors shall be free from the audited organisation's interference in determining the audit scope, conducting a pharmacovigilance system audit, and communicating the audit results. Key reporting shall be directed to top management of the audited organisation who has overall responsibility for the executive and management structure to enable the auditor to discharge his/her responsibilities and provide an independent and objective auditor's opinion. Auditors can consult with experts, personnel involved in pharmacovigilance processes, and the authorised pharmacovigilance officer while maintaining an unbiased attitude and not affecting the objectivity and quality of the work performed. To ensure objectivity, the auditor, when assessing audit facts, shall not take the point of view of the experts involved as a priority.

Auditors' Qualifications, Professionalism, Experience and Continuous Professional Development

208. Auditors shall have the required qualifications and maintain them in terms of the knowledge, skills and abilities necessary to effectively conduct pharmacovigilance system audit activities. Auditors shall have the skills, abilities, and knowledge in terms of:

a) audit principles, procedures, and methods;

b) existing regulatory legal acts, guidelines, and other requirements related to the pharmacovigilance system;

c) pharmacovigilance measures, processes, and procedures;

d) management systems;

e) organisational systems.

Quality Assessment of Audit Activities

209. Quality assessment of audit activities can be carried out through the ongoing and periodic assessment of all audit activities, reviews of the audited party, and self-assessment of audit activities (e. g., quality control of audit activities, adherence to the code of conduct, audit programs, and audit procedures).

5. Audits by External Audit Service Providers

210. The primary responsibility for the functioning and effectiveness of the pharmacovigilance system rests with the MA holder. If the organisation decides to use an external audit provider to fulfill the requirements for the pharmacovigilance system audit based on the relevant requirements of these Rules, the following requirements should be met:

a) the MA holder shall communicate the requirements for auditing and preparation of the audit risk assessment, audit strategy, audit program, and individual audit engagements to the external audit service providers in writing;

b) the MA holder shall communicate the scope of work, objectives, and procedural requirements for auditing to the external audit service providers in writing;

c) the organisation shall obtain documentary evidence of the independence and objectivity of external audit service providers;

d) an external audit service provider shall also comply with the relevant requirements given in these Rules.

6. Storing Audit Reports

211. Audit reports and information confirming the completion of audit actions shall be kept in accordance with the requirements specified in Section II of these Rules.

7. Requirements for Auditing

Marketing Authorisation Holders

212. MA holders are required to regularly conduct risk-based audits of their pharmacovigilance system, including an audit of the pharmacovigilance quality system, to ensure that the current quality system meets the requirements. The dates and results of the carried-out audits and surveillance audits shall be properly documented.

Authorised Pharmacovigilance Officer in the Member States

213. The authorised pharmacovigilance officer’s responsibilities in the Member States concerning audit activities are defined in Section II of these Rules. The authorised pharmacovigilance officer in the Member States shall report on the pharmacovigilance system audit results and provide information to auditors involved in risk assessment, including information on the status of implementation of corrective and preventive actions. The authorised pharmacovigilance officer in the Member States shall be informed of the results of any audit related to the pharmacovigilance system in the Member States, regardless of where it is carried out.

Authorised Authorities of the Member States

214. The Member State’s authorised authority shall regularly conduct independent audits of the objectives of the Member States’

pharmacovigilance system, regular audits of its pharmacovigilance system, and risk-based quality system audits to ensure that the quality system meets the requirements. The dates and results of the carried-out audits and surveillance audits shall be properly documented.

8. Adopted Methodology

215. To ensure a coordinated and harmonised planning and implementation of audits and preparation of their reporting, audits carried out in the Member States' authorised authorities shall be based on the terminology and methodology adopted by these Rules.

9. Requirements for Audit Reporting

MA holder's Reporting

216. The MA holder shall include an explanatory record concerning the critical and significant results of the pharmacovigilance system audit in the pharmacovigilance system master file. Based on the audit results, the MA holder shall ensure the preparation and implementation of an appropriate detailed corrective and preventive action plan. After completing corrective and preventive actions in full, the record in the master file can be deleted. Objective evidence is required to remove any audit-related information from the pharmacovigilance master file.

217. The MA holder shall ensure that a list of all scheduled and conducted audits is included in an annex to the pharmacovigilance system master file and that all scheduled audits are carried out in compliance with the reporting obligations specified in the legislation of the Member States, these Rules, and the internal rules applicable to reporting. The dates and

results of the carried-out audits and surveillance audits shall be properly documented.

Reporting of the Member States' Authorised Authorities

218. Authorised authorities of the Member States shall ensure that they ensure compliance with the reporting obligations on the audits performed in accordance with these Rules, Union authorities' acts, the Member States' legislation, and the internal rules applicable to reporting.

10. Privacy

219. The documents and information collected by the internal auditor shall be handled in accordance with the requirements of the legislation of the Member State, including in the field of the protection of personal data and confidential information.

VI. Risk Management System

1. General Provisions

220. The risk management process consists of the following interrelated and repetitive stages:

a) preparation of the characteristics of the safety profile of the medicinal product, with the definition of important identified, important potential risks and missing information, as well as aspects of the safety profile that require active management measures or further study (safety specification);

b) planning pharmacovigilance activities to characterize risks and identify new risks, as well as increase the general level of knowledge about the safety profile of a medicinal product (pharmacovigilance plan);

c) planning and implementing the activities to minimize risk consequences and assess the efficiency of these activities (risk minimisation measures plan).

221. Since there is an accumulation of safety data with an increase in knowledge on the safety profile of the medicinal product during the post-authorisation stage, appropriate changes are made to the risk management plan.

222. At the stage of getting marketing authorisation for a medicinal product, as well as other stages of the medicinal product's life cycle, the necessary additional measures may be determined to study safety or efficacy aspects or additional risk minimisation measures to ensure the use of the medicinal product when the benefit exceeds the risk, which shall be included in the risk management plan and implemented by the MA holder.

223. The requirements for the format of data presentation in the risk management plan are determined subject to ensuring their uniformity and compliance of the information provided with the requirements of these Rules.

2. Risk Management Principles

224. The main objective of the risk management process is to ensure that the drug is used with the greatest possible excess of the medicinal product benefit over the risks for each patient and target populations as a whole. Proper planning of the risk management system shall be ensured throughout the medicinal product's entire life cycle. The risk management system shall be proportional to the identified risks and potential risks of a medicinal product usage as well as the need to obtain safety data at the post-authorisation stage.

225. The risk management plan shall focus on the risks related to the risk management activities associated with the use of the authorised medicinal product.

The identified risk includes:

adverse reactions reliably demonstrated in preclinical trials and confirmed by clinical trial data, adverse reactions identified in well-designed clinical or epidemiological studies, where the degree of difference in the estimated parameter between the groups suggests a causal relationship, adverse reactions predicted based on data from several spontaneous reports with an appropriate level of documentation where the causal link is reliably confirmed by the temporal relationship and the biological or pharmacological mode of development;

adverse reactions included in Section 4.8 of the Summary of Product Characteristics unless they are the pharmacological class effects and are indicated in the summary of product characteristics but are not directly described for this medicinal product (in this case, such a risk is a potential risk).

The risk management plan shall consider those of the identified risks associated with the medicinal product use, which are related to adverse clinical outcomes for which there is sufficient scientific evidence of a relationship with the use of the medicinal product. Reports of adverse reactions may be obtained from numerous sources, such as preclinical (non-clinical) data, supported by clinical data, data from clinical and epidemiological studies, and sources of spontaneous reports, including data published in the scientific medical literature. Identified risks may be associated with the situations where a medicinal product is used not following the general characteristics of the medicinal product or the package insert, and medication errors or drug-drug interactions of this medicinal

product. Not all reported adverse reactions are necessarily assessed as a risk associated with the medicinal product use in a particular clinical context.

The risk management plan shall consider only those of the potential risks related to the medicinal product use, which are associated with adverse clinical outcomes and for which there is scientific evidence allowing suspecting the possibility of a causal link of a potential risk with the medicinal product use but in respect of which there is currently insufficient evidence to conclude that this causal link has been confirmed.

226. The risk management plan shall focus on important identified risks that may affect the risk-benefit balance of the medicinal product. As regards an important identified risk to be included in a risk management plan, it is generally necessary to:

a) perform further risk assessment as part of the pharmacovigilance plan (e. g., to study the frequency, seriousness, severity and outcomes of this risk when using the medicinal product in routine practice, as well as for populations most at risk);

b) implement the risk minimisation activities: inclusion in the information on the medicinal product, recommendations regarding certain clinical measures that need to be taken to minimize the risk, or take some additional risk minimisation measures.

227. Important potential risks to be included in the risk management plan are the risks that can affect the risk-benefit ratio of the medicinal product in case of their subsequent characterisation and confirmation. Where it is scientifically justified that an undesirable clinical result may arise from using the medicinal product not following its general characteristics or package inserts, using in populations not studied in clinical trials, or from long-term use of the medicinal product, the adverse reaction should be considered as a potential risk and if it is assessed as important, it should be included in the

list of safety concerns as an important potential risk. An important potential risk, which is included in a risk management plan, usually requires further assessment as part of a pharmacovigilance plan.

Examples of potential risks include:

the risks identified based on the results of preclinical toxicological studies that were not observed or were rejected according to the results of clinical trials;

adverse events observed in clinical or epidemiological studies in which the degree of difference in a risk parameter compared to a reference group (placebo, active ingredient, or untreated group) suggests the presence of a causal link but is not sufficient to confirm the presence of a causal link;

a signal received from the system for collecting spontaneous reports about adverse reactions;

a risk known as related to other active ingredients within one class, or the development of which is assumed based on the medicinal product's properties.

Missing information related to risk management planning is determined based on the area of lacking knowledge about the medicinal product safety for a particular intended use (for example, long-term use) or for use in specific patient populations for which there is insufficient knowledge to determine whether the safety profile differs from that currently characterised medicinal product's safety profile. The absence of data per se (e. g., the exclusion of a population from clinical trials) does not necessarily mean that it is a safety concern. Risk management planning in terms of missing information shall be focused on aspects of the medicinal product use, in respect of which a possible difference from the known safety profile of the medicinal product is expected. A scientific justification is needed to include a

specific population or aspect of the medicinal product use in a risk management plan as missing information.

228. The risk management plan is a dynamically changing document that shall be updated throughout the medicinal product's entire life cycle. The update of the risk management plan includes the inclusion of newly identified safety concerns in the risk management system and (as the safety profile is studied) the elimination or change of the classification assignment of safety concerns.

229. When determining the classification of risks, the following instructions should be used, aimed at continuous review and reduction of the list of safety concerns throughout the medicinal products' life cycle:

a) important potential risks can be excluded from safety specification of the risk management plan (e. g., in cases where the accumulated scientific and clinical data do not support the initial assumption regarding the impact on the person and the potential risk cannot be assessed as important;

b) in cases where there is no reason to believe that any pharmacovigilance activity may further complement the existing risk characterisation data) or their classification may be changed so that to refer them to important identified risks (e. g., if scientific and clinical data strengthen the evidence base to confirm the relationship between the risk and medicinal product use);

c) important identified risks may be excluded from the safety specification of the risk management plan under certain circumstances, where it can be demonstrated that the risk is fully characterised and adequately managed (e. g., for medicinal products that have been used for a long time, for which at the current stage any additional pharmacovigilance activities and /or recommended risk minimisation measures have become fully

integrated into standard clinical practice, for example, have been included in treatment protocols or clinical guidelines);

d) considering the general objective to obtain more information on the risk–benefit ratio for certain populations not included in the pre-authorisation study program for a medicinal product, relevant aspects of the information, which is missing in the list of safety concerns, may be excluded from the safety specification section as safety data are obtained at the post-authorisation stage or in cases where there is no reason to believe that the pharmacovigilance activity can currently or in the future complement existing risk characterisation data in terms of missing information.

230. Additional pharmacovigilance activities may be excluded from the risk management plan as they are implemented, except for some patient registries.

231. The need to continue implementing additional risk minimisation measures is subject to constant assessment with the determination of the required changes. If additional risk minimisation measures become part of routine practice (e. g., when recommendations for specific clinical risk minimisation or prevention measures are included in standard treatment protocols), additional risk minimisation measures may become routine when their effectiveness is confirmed. If the ineffectiveness of risk minimisation measures is revealed, a decision may be made to introduce more effective additional risk minimisation measures. Certain types of risk minimisation activities may be required throughout a medicinal product’s life cycle (e. g., pregnancy prevention programs).

3. Responsibility for Risk Management within the Organisation

232. The main participants in the process directly involved in planning the management of risks related to medicinal product use are the MA holders

and the Member States' authorised authorities responsible for regulating the circulation of medicinal products.

Marketing Authorisation Holders

233. As regards the risk management process, the MA holder is responsible for:

a) ensuring the functioning of an appropriate risk management system on the Member States territory in accordance with the requirements of the legislation of the Member States;

b) ensuring that a continuous critical assessment of all safety data obtained using a medicinal product is carried out. The MA holder shall ensure continuous monitoring of pharmacovigilance data to identify new risks, change available information on risks and change the risk–benefit ratio of medicinal products with a corresponding update of the risk management system and risk management plan in accordance with the requirements of this section of the Rules. A critical assessment of a medicinal product's safety profile shall be performed continuously and reflected in the data submitted in a periodic safety update report, regardless of the obligation to submit a risk management plan. In addition to the above conditions, two additional stages below are recommended for revising the risk management plan for medicinal products approved according to the marketing authorisation application on the initial submission of a complete marketing authorisation application, reflecting the need to make changes to the safety specification, planned and ongoing pharmacovigilance activities and risk minimisation measures:

upon confirming the authorisation (renewal) in 5 years after getting marketing authorisation;

during the submission of the first periodic safety update report after undergoing the renewal procedure.

It is assumed that this periodic safety update report is submitted after approval of renewal in accordance with the established submission schedule (approximately in 8 to 9 years after getting a marketing authorisation certificate) when the consideration of MA applications for generics with the corresponding active ingredient can begin. Therefore, by the said moment, the medicinal product's safety profile will in the majority of cases be sufficiently well characterised to allow a critical assessment and updating of the list of safety concerns.

Authorised authorities of the Member States

234. Obligations of the Member States' authorised authorities in relation to the risk management process are as follows:

a) continuous monitoring of the benefits and risks of medicinal product use, including the assessment of reports of identified adverse reactions submitted by MA holders, medical and pharmaceutical workers, patients and obtained from other sources of information (if necessary);

b) taking appropriate regulatory measures to minimize the risks associated with the medicinal product use and ensure that the maximum possible benefit is obtained from the use of medicinal products;

c) ensuring the implementation of measures to minimize risks;

d) effective exchange of data with stakeholders in the presence of new information available. This exchange includes providing information in an appropriate format to patients, medical and pharmaceutical professionals, patient groups, scientific communities, etc.;

e) ensuring that appropriate measures are taken to minimize risks (where introduced) by all MA holders concerning both original and generic, biosimilar medicinal products;

f) providing information to other authorised authorities of the Member States, including notification of any safety activities concerning the medicinal product, including notification of changes in the original medicinal product's information.

4. Risk Management Plan Objectives

235. The information contained in the risk management plan shall meet the following requirements:

a) determine and characterize the medicinal product's safety profile;

b) indicate how the further characteristics of the medicinal product's safety profile can be supplemented;

c) provide documentary evidence of the adopted measures to prevent or minimize the risks associated with using a medicinal product, including an assessment of the measures' effectiveness;

d) provide documentary confirmation of the performed post-authorisation obligations to ensure the safe use introduced during a medicinal product authorisation.

236. The risk management plan shall specify the degree of confidence that the efficacy of the medicinal product will be the same as in clinical trials.

5. Overview of the Risk Management Plan Format and Content

237. The risk management plan consists of 7 parts. The submitted risk management plan shall have a consistent template to enable the risk management plan assessment.

Part II of the Risk Management Plan — Safety Specification— is subdivided into several modules, which allows the content of the section to be adapted to a medicinal product's specificity. The modular structure is

intended to facilitate the updating of the risk management plan, to enable the application of simplified requirements for the content of certain modules; however, the plan shall be presented as a single document, including all modules and annexes in accordance with the relevant requirements of this section of the Rules.

The risk management plan includes the following parts and modules:

Part I: Medicinal Product Overview Information;

Part II: Safety Specification;

Module CI: Epidemiology of Indications for Target Populations;

Module CII: Preclinical Part;

Module CIII: Drug Exposure during Clinical Trials;

Module CIV: Populations Not Examined in Clinical Trials;

Module CV: Post-authorisation Experience;

Module CVI: Additional Requirements for the Safety Specification;

Module CVII: Identified and Potential Risks;

Module CVIII: Summarised Safety Information;

Part III: Pharmacovigilance Plan;

Part IV: Plan for Post-authorisation Efficacy Studies;

Part V: Risk Minimisation Measures (Including Evaluation of Risk Minimisation Measures' Effectiveness);

Part VI: Summary of the Risk Management Plan;

Part VII: Annexes.

238. The amount of information, especially in part II of the risk management plan, shall be proportional to the identified and potential risks; it also depends on the type of medicinal product, the risks associated with its use, and the stage of the medicinal product's life cycle.

239. The risk management plan for advanced therapy medicinal products shall consider the special requirements determined for this group of

drugs concerning support at the post-authorisation stage, taking into account their characteristics. The specific requirements for a risk management plan for advanced therapy medicinal products should be agreed upon with the Member State's authorised authority before applying for marketing authorisation as part of the scientific consultation procedure. When developing a risk management plan for advanced therapy medicinal products, additional requirements for the risk management system, post-authorisation monitoring of this group of pharmaceuticals' efficacy and safety, determined by the acts of the Union, should be taken into account.

240. If the MA holder has more than one medicinal product containing a similar active ingredient(s), it is recommended that all relevant medicinal products be included in the risk management plan (therefore, a risk management plan is developed for an active ingredient).

241. Information in the risk management plan shall be provided in sufficient detail; still, it is not allowed to include unnecessary text that is not directly related to the information in the document and distracts from the critical aspects of the information presented, which shall be taken into account when forming a risk management plan associated with the product use. The risk management plan shall contain a comprehensive overview, assessment, and discussion of the risks associated with the use of a product, with an emphasis on the most important risks that have been identified or are expected from the assessment of preclinical, clinical, and post-authorisation data presented in other modules of the marketing authorisation application. Any data included in the risk management plan shall be consistent with the information provided elsewhere in the marketing authorisation application. The risk management plan shall include references or links to the relevant sections of the preclinical and clinical reviews and summaries presented in the marketing authorisation application.

242. In order to ensure consistency between the information provided in the marketing authorisation application and the risk management plan where this plan is submitted as part of the marketing authorisation application for the medicinal product, it is necessary account for the relationship between the information provided in the sections of the risk management plan and in the modules of the marketing authorisation application for the medicinal product in accordance with Table 1.

Table 1

Correspondence between the sections of the risk management plan and the modules of the marketing authorisation application

Section of the risk management plan	Module of the marketing authorisation application
Part I: Medicinal Product Overview Information	Module 2.3: General Summary on Quality Module 3: Quality
Part II, Module CI: Epidemiology of Indications for Target Populations	Module 2.5: Clinical Data Review
Part II, Module CII: Preclinical Part	Module 2.4: Review of Preclinical Data; Module 2.6: Summary of Pharmacological Data in Text Format and in the Form of Tables; Module 4: Non-Clinical (Preclinical) Reports
Part II, Module CIII: Medication Exposure in Clinical Trials	Module 2.7: Summary of Clinical Data; Module 5: Clinical Trials Reports
Part II, Module CIV: Populations Not Examined in Clinical Trials	Module 2.5: Clinical Data Review
Part II, Module CV: Post-authorisation Experience	Module 2.5: Clinical Data Review
Part II, Module CVII: Identified and Potential Risks	Module 2.5: Clinical Data Review (Including the Conclusion on the Benefit-Risk Ratio Assessment); Module 2.7: Summary of Clinical Data (Summary of the Medicinal Product Characteristics)

Section of the risk management plan	Module of the marketing authorisation application
Part II, Module CVIII: Summarised Safety Information	Module 2.5: Clinical Data Review; Module 2.7: Summary of Clinical Data
Part III: Pharmacovigilance Plan	Module 2.5: Clinical Data Review; Module 2.7: Summary of Clinical Data
Part IV: Plan for Post-authorisation Efficacy Studies	Module 2.5: Clinical Data Review; Module 2.7: Summary of Clinical Data
Part V: Risk Minimisation Measures (Including the Assessment of Risk Minimisation Measures' Effectiveness)	Module 2.5: Clinical Data Review; Module 2.7: Summary of Clinical Data

243. Using information from the modules of marketing authorisation application refers to cases of submission for registration of a marketing authorisation application for a medicinal product where a risk management plan is included in the number of documents (for example, filing an application for granting a marketing authorisation or making significant changes) or to the data previously presented in the marketing authorisation application.

244. Description of the content of the sections and modules of the risk management plan in accordance with paragraphs 246–347 of these Rules contains recommendations on the basic data to be presented in the document. It should be considered that some aspects of the data provided if they are not related to a particular medicinal product, can be reduced; conversely, it may be necessary to highlight additional aspects that are not mentioned in these Rules. All information presented in the risk management plan shall be scientifically substantiated; it is not allowed to include information elements of an advertising nature.

245. The section of the risk management plan preceding the main document shall include the following administrative information:

a) data lock point of the current risk management plan;

b) date of signing and version number of the risk management plan;

c) list of parts and modules. For updates to the risk management plan, the said section of the risk management plan shall include in tabular form the version number of the modules and the date of approval by the MA holder. If an updated version of the risk management plan is submitted, a commentary is included with a summary of the justification for updating the risk management plan and a summary of significant changes to the sections of the risk management plan.

d) Confirmation of the review and approval of the risk management plan by the authorised pharmacovigilance officer in the form of the actual signature of this person or other evidence of approval of the submitted version of the risk management plan by the authorised pharmacovigilance officer. If the risk management plan is submitted as part of the marketing authorisation application; as confirmation of control by the authorised pharmacovigilance officer, a statement may be submitted that the risk management plan has been reviewed and approved by the authorised pharmacovigilance officer of the MA holder and the document is certified with an electronic signature.

6. Detailed Description of Each Part of the Risk Management Plan

Part I: Medicinal Product Overview Information

246. This part shall contain administrative information about the risk management plan and overview information on the medicinal product(s) for which the risk management plan is drawn up. The information provided shall be up-to-date and accurate in terms of the current application for marketing

authorisation of a medicinal product as it will be reflected in the marketing authorisation certificate.

The specified part shall contain the following information:

information about an active ingredient:

active substances (active ingredients) of the medicinal product(s);

pharmacotherapeutic group (ATC Code);

name of the planned MA holder;

the name and form of the medicinal product release for which this risk management plan has been developed;

information on the authorisation procedure (mutual recognition, decentralised, in accordance with the Member State's legislation);

trade name in the Member States;

a summary of the medicinal product (including its chemical class, a summary of the mode of action, important information about its composition (e. g., the origin of the active ingredient of biological medicinal products, appropriate adjuvants for vaccines));

reference to the section of the marketing authorisation application that contains information about the medicinal product (if applicable);

indications (approved and proposed) (where applicable);

dosage regimen (brief information on the main target population without duplicating Section 4.2 of the Summary of Product Characteristics);

information on dosage forms and strength;

an indication of the medicinal product's status subject to additional monitoring (when deciding on authorisation or at the stages of updating the risk management plan).

Part II: Safety Specification

247. This part shall provide a brief overview of the medicinal product's safety profile, highlighting those safety aspects that require further risk management action. The safety specification shall summarize the important identified risks of a medicinal product, important potential risks, and missing information. The safety specification shall also describe the population groups that potentially represent risk groups (when the drug is used both according to and not following the summary of product characteristics) and all insufficiently studied aspects of the safety profile that require further study at the post-authorisation stage to clarify and form a correct assessment of the product's risk–benefit ratio. The safety specification in terms of risk management forms the basis of the pharmacovigilance plan and risk minimisation plan.

The safety specification in terms of risk management includes 8 modules in accordance with paragraph 237 of these Rules.

248. MA holders are encouraged to follow the specified structure of the safety specification. The safety specification may include additional elements depending on the properties of a medicinal product, its development, and study programs, including quality aspects and their impact on the safety and efficacy profile of the medicinal product, the risk associated with the dosage form, and other aspects modifying the safety profile.

General Guidelines for Generic and Advanced Therapy Medicinal Products

Generic Medicinal Products

249. For generics, it is assumed that the safety data sheet will comply with the safety data sheet for the reference medicinal product or other

generics; there is an approved safety specification in force. In case of inconsistencies between the approved risk management plans for similar medicinal products, the MA holder shall propose and justify a safety specification that corresponds to this generic. In exceptional cases, if there are appropriate grounds, a safety specification may be submitted for a new generic with differences in terms of safety concerns compared to the safety profile of the reference medicinal product (e. g., in the case when for the reporting period, based on the obtained data there have been changes in the assessment of the safety profile of the product; if there are differences in the characteristics of the generic compared to the reference product, for example, if there is a risk associated with an excipient present only in some products).

Advanced Therapy Medicinal Products

250. According to the legislative acts of the Union, advanced therapy medicinal products include gene therapy products, somatic cell products, and tissue-engineered products.

251. Due to their specific nature, advanced therapy medicinal products are characterised by special risks, which, as a rule, are not inherent in other pharmaceuticals. These particular risks include risks to living donors, risks of cell line transformation, and the transfer of vectors. These specific risks shall be taken into account when developing a safety specification for advanced therapy medicinal products.

Module CI: Epidemiology of Indications for Target Populations

252. The description and assessment subject of this module is the epidemiology of indications. The description shall include an assessment of incidence, prevalence, mortality, data on outcomes in the absence of target

population treatment, information on common comorbidities in the target population. The description shall be stratified by age, gender, and racial and/or ethnic origin in the event that the specified population aspects of the characteristic are significant for safety assessment and risk management.

253. Differences in epidemiology of indications across regions shall also be assessed and described (where regional differences are characteristic of epidemiology). In case the Member States have different characteristics of the epidemiology of indications, a description of these differences may be provided in the part of Annex 9 of the risk management plan referred to in paragraph 344 of these Rules, following such data format and structure.

254. Information should also be provided on the risk factors for the disease and the main existing treatment approaches. The module includes information on significant (relevant) adverse events expected (in the absence of treatment) in the target population, including the frequency and characteristics of adverse events. The data provided in the module shall help predict and interpret potential signals and determine the directions for minimizing risks. The information shall be brief, accurate, and shall not contain advertising elements.

Module C II: Preclinical Part

255. This module shall contain a summary of important findings from preclinical safety studies, for example:

a) toxicity study results (key data about toxicity obtained during the studies, for example, toxicity with single and repeated (multiple) use, reproductive toxicity, embryotoxicity, teratogenicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);

b) data on pharmacological safety studies (e. g., effects on the cardiovascular system, including prolongation of the QT interval, the nervous system, etc.);

c) data on the medicinal product interactions;

d) other toxicity data.

256. The module shall provide information on the significant toxic properties and the relevance of the findings when a product was used in humans. The data's significance will depend on the medicinal product properties, the characteristics of the target population, and the experience of using similar compounds or approaches to therapy when using products of the same group. It is necessary to reflect the established significant directions of toxic effects (for target systems and organs) and a reasonable assessment of the obtained data on toxicity to humans. Besides, quality aspects shall be discussed if they can significantly affect the medicinal product's safety profile (particularly, important information about the active ingredient or its impurities, for example, genotoxic impurities). If the medicinal product is intended for use by women of childbearing age, the document must provide data on reproductive toxicity and effects on fetal development, as well as on the consequences of using the product in this patient group.

257. If preclinical (non-clinical) safety data imply an important potential risk to the target population, the relevant risk should be included as a safety concern in Module CVIII of the safety specification of the risk management plan.

258. Aspects of toxicity identified in preclinical (non-clinical) studies assessed as not significant in human use shall be appropriately justified for the assessment performed and shall not be included as safety concerns in Modules CVII and CVIII.

259. If based on the results of preclinical (non-clinical) or clinical trials, it is determined the need for additional preclinical (non-clinical) studies with the inclusion of these studies in the pharmacovigilance plan, the module includes brief information with justification of such need and indication of the planned measures.

260. Conclusions for this section shall be consistent with the content of Module CVII, and any identified safety concerns shall be reflected in Module CVIII.

261. The content of this module shall be assessed in terms of compliance with the updated level of knowledge about the medicinal product throughout its life cycle. At the post-authorisation stage, this section is subject to update in the case when, based on the new data obtained from preclinical (non-clinical) studies, changes to the list of safety concerns are required. Safety concerns detected based on data from preclinical (non-clinical) studies, which over time are not assessed as relevant, or have not been confirmed based on the results of obtaining sufficient and appropriate experience of use at the post-authorisation stage or based on the generated evidence base, can be excluded from the list of safety concerns.

Module CIII: Drug Exposure during Clinical Trials

262. To assess the limitations of safety data obtained from studies with human participation, the module shall provide data on patients included in clinical trials (in which patient groups the product was studied). The data shall be presented in a format suitable for analysis, for example (e. g., in the form of tables or graphs). Clinical study data are reported before the time of the initial submission of the risk management plan or significant changes to the module due to the update of data on exposure assessment during clinical trials (e. g., for new indications). The content of this module shall be assessed

for compliance with the real-time data throughout the product life cycle; in the absence of new significant data on the medicinal product’s exposure during clinical trials, updating of this module is not required.

263. The size of the studied population should be described in detail, indicating the data on the number of patients and the period (in the form of patient-years, patient-months) during which patients were exposed to the medicinal product (where applicable). Data on populations included in clinical trials shall also be reported stratified. The stratification of population subgroups in such cases, as a rule, includes:

a) age and gender;

b) indications;

c) strength;

d) stratification by other criteria can be given if it is relevant to the planning of the risk management system (e. g., race).

264. When reporting age data, categories that are relevant to the target population shall be selected. Data for pediatric and elderly patients shall be separated according to accepted age categories (e. g., 65 to 74, 75 to 84, and over 85 for elderly patients).

265. Except where necessary, data on clinical trials shall be presented summarised, not for individual clinical trials, with the summation of indicators by columns and sections (if justified). If the same group of patients was included in more than one study (e. g., continued open observation after the end of a clinical study), it is included in the table by age, gender, and race once. If there is a discrepancy between the tables in terms of the number of patients, appropriate explanations shall be given.

266. Where a risk management plan is submitted with an application for a new indication for medicinal product use, new dosage form or route of

administration, the details of the change shall be presented separately at the beginning of this module and in the summary tables.

Module CIV: Populations Not Examined in Clinical Trials

267. This module of the safety specification of the risk management plan is intended to describe populations that are considered in the context of missing information. This module shall provide information on which specific patient subgroups of target populations have not been studied or have been studied only to a limited extent within patient groups included in clinical trials (e. g., pregnant women, women who breastfeed, pediatric population, elderly patients, patients with renal failure, impaired liver function or cardiovascular disorder, populations with corresponding genetic polymorphisms, patients with immunosuppression, and populations of different ethnicities, patients whose disease severity differs from that analysed in clinical trials). Where applicable, the degree of renal, hepatic, or cardiovascular impairment in the population subgroup should be indicated, and the type of genetic polymorphism that constitutes the limitation of the examination in clinical trials. Clinical Trials' limitations shall also be presented in terms of the relevance of inclusion and exclusion criteria to target populations and differences that may arise depending on the study parameters (e. g., hospital or ambulance practice). Conclusions about the predictability of safety for target populations shall be based on an accurate and detailed assessment of the limitations of available clinical study data, or lack thereof for any subgroup.

268. Suppose post-authorisation use of a medicinal product is expected in populations that have not been studied in clinical trials and proceeding from evidence-based data, a difference in the safety profile of these population groups from the target population is suspected, at the same time;

in that case, the available information is insufficient to determine whether such use of a medicinal product poses a safety concern, the use of medicinal product in these unstudied populations shall be included in the risk management plan as missing information. Data on populations excluded from the clinical development program shall be included in the missing information if a medicinal product is prescribed to patients in these groups following the approved and proposed indications; using the product in such populations may be associated with clinically significant risks. When determining differences between target populations and populations that were included in a clinical trial, it shall be noted that specific differences may arise due to differences in the location of the study (e. g., hospital or ambulance practice) and not due to particular inclusion or non-inclusion criteria. Where it is proposed to attribute population data to missing information, the rationale for the relevant subpopulation shall be included in Module CIV of the Risk Management Plan.

269. If there is evidence that there is a risk of adverse clinical outcomes when using a drug in populations that have not been included in clinical trials, this risk shall be included in the list of important (potential) risks.

Module CV: Post-authorisation Experience

270. This module presents the available data on the results of post-authorisation use in the territories of the countries where this medicinal product is authorised. The information in this module shall be provided in the form of the post-authorisation experience review, which may be helpful for risk management planning purposes. The data presented in the section shall not fully duplicate information from a periodic safety update report.

271. The module shall include information reflecting the assessment of the practical use of the medicinal product and aspects of use following or not

following the summary of product characteristics, including in the case when it is necessary to identify risks in Module CVII and assessment of use in special populations indicated in Module CIV.

272. The module shall provide cumulative data on the medicinal product use in the third countries' territories following the therapeutic indications that are not approved in the Member States (if applicable and relevant in the context of Module CVII), and the impact of these aspects on the medicinal product use in the Member States' territories.

Module CVI: Additional Requirements for the Safety Specification

273. The module shall provide an assessment of the potential for the risk of the medicinal product misuse for illegal purposes and suggest risk minimisation measures, for example, reducing the size of the package, introducing a controlled access program, and special requirements for the prescription of the product (if applicable).

Module CVII: Identified and Potential Risks

274. This module of the risk management plan contains information on important identified and potential risks and missing information (information on safety concerns).

275. The following aspects of the safety profile require a special assessment to determine the risks of a medicinal product; such assessment shall be provided in the module in case these aspects pose risks when using the medicinal product:

a) the potential risk of overdose, both intentional and accidental, for example, in cases where a medicinal product has a narrow therapeutic interval or can cause severe dose-dependent toxic reactions and/or is

characterised by a high risk of intentional overdose in the target population (e. g., patients with depression). If overdose cases with adverse consequences for the patient have been identified in clinical trials, an appropriate indication shall be made in the risk description, and important risks due to overdose shall be included as safety concerns in Module CVIII of the safety specification with the proposal of appropriate risk minimisation measures in Part V of the risk management plan (if necessary);

b) potential risks arising from medication errors are defined as an unintentional error in therapy that harms or may harm a patient. If in the course of clinical trials at the stage of medicinal product development, medication errors were identified that led to important risks, the module provides information on these errors, including the potential cause and possible ways to eliminate them. If applicable, indicate how these data were taken into consideration during the finished product development. Evaluation, presentation and subsequent organisation of work with medication errors in the risk management plan shall be based on appropriate approaches to minimize risk and prevent errors in the use of the medicinal product. If at the post-authorisation stage important risks associated with medication errors are identified, a risk assessment shall be presented in the update of the risk management plan and measures to minimize the risk medication errors shall be proposed;

c) The potential risk of transmission of infectious agents associated with the nature of the manufacturing process or the materials used. For live attenuated vaccines, any potential risk of transmission of mutated live vaccine virus should be considered, and the potential risk of infection in immunocompromised patients by exposure to the vaccine, which could be assessed as an important potential risk.

d) The potential risk of out-of-specification use in cases where a difference in safety concerns is expected between the target population and the population to which the medicinal product is not administered according to the summary of product characteristics. Potential risks arising from the use of a medicinal product not following the summary of product characteristics shall be considered for inclusion in the safety specification.

e) For important identified or potential risks that are pharmacological class effects, if these risks are not assessed as important for the relevant medicinal product, evidence should be provided to support the assessment and conclusion;

f) important risks associated with the identified and potential pharmacokinetic and pharmacodynamic drug interactions shall be considered in the light of established treatment approaches for approved indications and considering the commonly used medicinal products in the target population. It is necessary to present cumulative data confirming the drug interaction and the possible mode of drug interaction, the possible risks to patients' health when used for various indications and in different populations, and plans for the further characterisation and minimisation of the described risks. Important risks arising from drug interactions shall be included in safety concerns;

g) risks for pregnant and breastfeeding women (e. g., teratogenic risk-direct or indirect through exposure to semen): contraceptive recommendations can be considered risk minimisation measures;

h) risk of affecting fertility-appropriate measures should be taken to minimize the risk, such as routine risk communication and /or additional measures to maintain fertility: semen cryopreservation in men and cryopreservation of embryos and oocytes women;

i) risks associated with the disposal of the used product (e. g., transdermal patches with the residual active ingredient or residual amounts of radioactive diagnostic agents);

j) risks associated with the product administration procedure (e. g., risks associated with the use of a medical device, such as malfunctions affecting the administered dose);

k) pediatric safety aspects considered as a safety concern for the pediatric population.

276. If a MA holder does not provide an assessment of the above risks and comments regarding the justification for excluding these risks from the list of important identified or important potential risks, authorised authority has the right to request to supplement the module with an assessment of these risks.

277. When developing safety specifications of the risk management plan for advanced therapy medicinal products, risks specific to this drug group shall be considered.

Module CVII: Identified and Potential Risks. Section: Safety Concerns Identified for a Medicinal Product during the Initial Risk Management Plan Submission

278. This module shall contain a list of safety concerns identified for a medicinal product at the stage of initial submission of the risk management plan for obtaining a marketing authorisation application, or at the post-authorisation stage (for authorised medicinal products that did not previously have an agreed risk management plan). This module is formed following the approved initial version of the risk management plan and is not subject to subsequent changes.

Module CVII: Identified and Potential Risks. Sections: Risks Rated as Important for Inclusion in Safety Concerns and Risks Not Rated as Important for Inclusion in Safety Concerns

279. This module shall provide information characterizing risk severity, frequency, and impact on the risk–benefit ratio of the medicinal product.

280. In terms of risks that are not related to safety concerns, information can be combined following the grounds according to which these risks are not classified as safety concerns.

Module CVII: Identified and Potential Risks.
Section: New Safety Concerns and Reclassification of Safety Concerns in Risk Management Plan Update

281. According to the safety data obtained at the post-authorisation stage, information on new identified and potential risks is included in the documents and safety sections of the marketing authorisation application (e. g., assessment of signals, periodic assessment of the risk–benefit ratio of the medicinal product, or procedures for making changes in the safety data) while performing the assessment grounds for classifying these risks as important and for including a risk management plan in the safety specification. In this case, the risk management plan does not require duplication of the presented data. Details of any new important identified or potential risks shall be reported in the Details of Important Identified Important Potential Risks and Important Missing Information sections of Module CVII of the Safety Specification of the Risk Management Plan specified in paragraphs 283–285 of these Rules.

282. If a change in the classification assignment or exclusion from the list of safety concerns of important identified or important potential risks in this module, it is necessary to justify this change and provide an appropriate reference to the safety data. Information in this section may be presented as a

description of a previous request from the authorised authorities with reference to the procedure in which such a request was made.

Module CVII: Identified and Potential Risks. Section: Details of Important Identified, Important Potential Risks, and Important Missing Information

283. Where the risk management plan is developed for a combination of medicinal products with significant differences (e. g., differences in fixed doses), it is necessary to clearly indicate which safety concerns apply to each drug in the combination.

284. This section of the risk management plan applies to all stages of the product life cycle. The reporting of important identified and important potential risks shall include the following information:

a) risk name (using the terminology of the international dictionary of adverse reactions arising from the use of medicinal products (MedDRA) (where applicable));

b) potential mode of action;

c) source of evidence and degree of evidence (scientific basis for suggesting a relationship);

d) risk profile (frequency, absolute risk, relative risk, seriousness, severity, reversibility, long-term outcomes, impact on life quality);

e) risk factors and risk groups (including patient-related factors, dose, risk period, additive or synergistic factors);

f) preventability (risk predictability, the presence of established risk factors that can be minimised through routine or additional risk minimisation measures, in addition to generating overall risk awareness by including information in the summary of product characteristics or package inserts; the stage of implementation, which can reduce the adverse reaction seriousness);

g) significant impact on the risk–benefit ratio of the medicinal product;

h) public health impact (health of population) (e. g., the absolute risk concerning the size of the target population and, accordingly, the actual number of adversely affected persons, or the overall result of general population exposure).

285. Information about missing data includes the following:

a) name of missing information (using MedDRA terminology (if applicable));

b) justification of the assumption that the safety profile differs in terms of missing information from the safety profile, which is characteristic of the general target population;

c) description of the population for which additional data on the safety characteristics is required, or a description of the expected risk in an unstudied part of the population, depending on the situation.

Module CVIII: Summarised Safety Information

286. Module CVIII of the risk management plan contains summarised information about the identified safety concerns classified according to the following categories:

a) important identified risk;

b) important potential risk;

c) important missing information.

Part III: Pharmacovigilance Plan

287. The purpose of the pharmacovigilance plan is to provide an overview and justification of the MA holder’s planned actions to characterize

further the safety concerns included in the safety specification. A pharmacovigilance plan is a structured plan designed for:

a) studying the potential risk to confirm the risk as identified or excluded from the list of safety concerns;

b) further characterisation of safety concerns (including severity, frequency, and risk factors);

c) determining the methods for obtaining missing information;

d) assessing the effectiveness of risk minimisation measures.

288. The pharmacovigilance plan shall not include any activities aimed at reducing, preventing or managing risks. These activities shall be presented in Part V of the risk management plan.

289. The pharmacovigilance plan shall focus on the safety concerns summarised in Module CVIII of the safety specification of the risk management plan and shall be comparable with the medicinal product's benefits and risks. If in doubt, marketing authorisation holders should have preliminary consultations with the Member State's authorised authority as part of the scientific consultation procedure regarding the need for additional pharmacovigilance measures, their main stages and deadlines.

290. Pharmacovigilance activities are subdivided into routine pharmacovigilance activities and additional pharmacovigilance activities.

Routine Pharmacovigilance Activities

291. Routine pharmacovigilance activities are a set of basic activities that shall be regularly performed by a MA holder for all medicinal products to ensure compliance with the requirements of the Member States' pharmacovigilance legislation. As part of routine pharmacovigilance activities, signal detection is an important element in identifying new medicinal products' risks. The pharmacovigilance system master file contains

detailed information on the routine pharmacovigilance measures of MA holders; there is no need to duplicate this information in the risk management plan.

292. The Member State's authorised authority has the right to suggest a MA holder supplement the current procedures for collecting, verifying, evaluating, and submitting information on adverse reactions performed as part of spontaneous reporting. Where this recommendation is limited to collecting additional structured data resulting from the assessment of the condition of a patient with an adverse reaction performed as part of routine clinical practice, this activity will be considered routine one. In this case, in this section of the risk management plan, the MA holder explains the changes in routine pharmacovigilance activities introduced according to the proposals of the Member State's authorised authority.

293. Where the authorised authority recommends to include the submission of tissue or blood samples to a designated clinical laboratory to assess additional parameters (e. g., determination of antibodies), which are not performed as part of routine clinical practice, this activity shall be considered as an additional pharmacovigilance activity.

294. This section of the risk management plan shall describe only routine pharmacovigilance activities beyond the activities performed to deal with adverse reaction reporting and signal detection.

Special Questionnaires for the Subsequent Collection of Information on Adverse Reactions

295. If to perform routine pharmacovigilance activities, a MA holder is required or plans to compile special questionnaires to obtain structured information on the identified suspected adverse reactions of particular interest, it is necessary to describe the use of the said materials as part of

routine pharmacovigilance activities and submit draft questionnaires in Annex 4 to the risk management plan. The use of special questionnaires for the subsequent collection of information on adverse reactions is one of the routine pharmacovigilance activities.

296. Without compromising the format originality, the questionnaire used by different MA holders for the same adverse event shall be as similar as possible to provide formation of consistent data for assessment and regulatory decision-making while reducing the burden on healthcare professionals. Based on this, MA holders should provide available special questionnaires upon request for other MA holders to examine and use them.

Other Routine Pharmacovigilance Activities

297. This section of the risk management plan shall include a description of other routine pharmacovigilance activities, (e. g., an enhanced passive monitoring program, analysis of observed versus expected data, cumulative reviews of adverse events of particular interest).

Additional Pharmacovigilance Activities

298. In this section of the risk management pan, a MA holder describes the planned additional pharmacovigilance activities, specifying what information shall be collected for the subsequent more informed assessment of the risk–benefit ratio. The MA holder should assess situations in which additional pharmacovigilance activities are required due to the inability to achieve the objective of properly assessing and studying the risk using routine pharmacovigilance methods.

299. Additional pharmacovigilance activities include pharmacovigilance activities that are not routine. This activity includes

preclinical trials, clinical trials and non-interventional studies, including long-term follow-up of patients participating in a clinical study, or a cohort study to assess the safety of a medicinal product in long-term use. If there is any doubt about the need to take additional pharmacovigilance activities, the MA holder can apply for consultation on this issue to the Member State's authorised authority within the framework of the scientific consultation procedure.

300. Studies in a pharmacovigilance plan shall focus on identifying and characterizing risks, collecting additional data on aspects of missing information, or evaluating the effectiveness of additional risk minimisation measures.

301. Study protocols can only be included in updating the risk management plan if the study data has been included in the pharmacovigilance plan and requested by an authorised authority. An overview and approved protocols of studies included in the pharmacovigilance plan shall be submitted in part B of Annex 3 to the risk management plan specified in paragraphs 334 and 335 of these Rules (through electronic references or links to the protocol included in another section of the electronic marketing authorisation application). Other protocols of category 3 studies specified in paragraph 304 of these Rules that are submitted for information only may also be included in part B of Annex 3 to the risk management plan specified in paragraphs 336 and 337 of these Rules. Once the final report is submitted for assessment to the authorised authority, the protocols of completed studies are subject to exclusion from Annex 3 to the risk management plan, while the studies are excluded from the pharmacovigilance plan.

302. MA holders can submit to the Member States' authorised authorities the protocols of post-authorisation safety studies for obtaining scientific advice.

Summary Table of Additional Pharmacovigilance Activities

303. This section of the risk management plan describes pharmacovigilance activities to identify and characterize the risks associated with medicinal product use. Some of these activities may be an obligatory requirement for authorisation because they are either key to the risk–benefit ratio of a medicinal product (specified as Category 1 studies in the pharmacovigilance plan) or specific obligations in the context of conditional authorisation under exceptional terms (specified as Category 2 studies in the pharmacovigilance plan). If the specified condition or obligation constitutes a non-interventional safety study, the implementation of this study is subject to control by an authorised authority and, when planning and conducting the study, the MA holder shall ensure that the requirements determined in Section X of these Rules are met.

304. In the risk management plan, other studies may be required to investigate the safety concern or evaluate risk minimisation measures' effectiveness. Such studies included in the pharmacovigilance plan also have a legal basis (specified as Category 3 studies in the pharmacovigilance plan). The summary table of the additional pharmacovigilance activities shall provide clarity to all interested parties as to what category an event in the pharmacovigilance plan refers under paragraph 303 of these Rules and this clause (condition for authorisation, a certain obligation, or study is necessary to analyze a safety concern further or to assess the effectiveness of risk minimisation measures, status (mandatory or legally justified), type of study

(interventional or non-interventional)). When conducting interventional studies, one should be guided by the Rules of Good Clinical Practice.

305. The risk management plan for generics shall reflect the need to perform pharmacovigilance studies, if such need exists at the time of authorisation. In certain cases, ongoing or planned post-authorisation safety studies for a reference medicinal product may be required for a generic medicinal product, for example, when it is necessary to include a larger number of patients in this study or all patients who have been prescribed treatment with a reference or generic medicinal product. Where applicable, joint post-authorisation safety studies are encouraged (e. g., when introducing a register or determining the requirements for conducting this study for all authorised medicinal products with a specific active ingredient and used for a specific indication).

Part IV of the Risk Management Plan: Post-Authorisation Efficacy Study Plan

306. This section of the risk management plan shall include a list of post-authorisation efficacy studies with a specific obligation or condition for authorisation. If the MA holder does not have any specific obligations during marketing authorisation, Part IV of the risk management plan may be left blank.

Part V: Risk Minimisation Measures (Including Assessment of Risk Minimisation Measures' Effectiveness)

307. In accordance with the safety specification, the marketing authorisation must assess what risk minimisation measures are required for each safety concern. The risk minimisation plan shall include details of the

risk minimisation measures to mitigate the risks associated with each identified safety concern.

308. For similar active ingredients in different medicinal products with significantly different indications or target populations, it is expedient to develop individual plans to minimize the risk for each of the products. That is, for medicinal products, whose indications for the use relate to different fields of medicine and are associated with various safety concerns or for medicinal products that cause different risks depending on the target population or for medicinal products with different prescription status, it is reasonable to develop individual risk minimisation plans.

309. Risk minimisation measures may consist of routine risk minimisation measures and additional risk minimisation measures. All risk minimisation measures shall have a clearly defined objective.

310. MA holders shall periodically assess the need to continue implementing the established risk minimisation measures and assess their effectiveness. Additional risk minimisation measures and assessment of the effectiveness of risk minimisation measures are described in detail in Section XII of these Rules.

Routine risk Minimisation Measures

311. Routine risk minimisation measures include activities (actions) carried out for each medicinal product. Routine measures apply to:

the summary of product characteristics and package insert (leaflet);

labeling of a medicinal product;

package size;

prescription status of a medicinal product.

It should be considered that the dosage form can also play an important role in minimizing the medicinal product’s risk.

Summary of Product Characteristics and Package Insert

312. Summary of product characteristics and package inserts are essential tools for minimizing risks since they represent a controlled and standardised format for sharing product-related information with medical and pharmaceutical workers and patients.

313. Summary of product characteristics and package inserts provide information on recommendations for routine risk minimisation measures; this information includes two types of recommendations:

routine risk communication is based on the information included in Subsection 4.8 of Section 4 of the summary of product characteristics and the package inserts, aimed at informing healthcare professionals and patients about the adverse effects of the medicinal product to decide on treatment subject to the safety profile data;

Routine risk minimisation measures include specific clinical measures aimed at preventing or reducing the risk and are reflected mainly in Sections 4.2 and 4.4 of the Summary of Product Characteristics; still, they may also affect Subsections 4.1, 4.3, 4.5, 4.6, 4.7, and 4.9 of Section 4 of the summary of product characteristics, as well as Sections 2 and 3 of the package inserts. Special instructions and precautions in the summary of product characteristics, aimed at minimizing the risk, include, in particular, the following information:

performing certain tests before starting treatment;

monitoring of laboratory findings during the treatment;

monitoring of symptoms and parameters specific for the risk manifestation;

dose adjustment or treatment discontinuation in case of adverse events or changes in laboratory findings;

performing an accelerated drug elimination procedure after treatment discontinuation;

recommendation on contraception;

prohibition of the simultaneous use of other medicinal products;

impact on risk factors that can lead to an adverse reaction when using a medicinal product;

recommendations for long-term follow-up clinical observation for early detection of delayed adverse reactions.

Packing Size

314. Planning the packaging size to limit the available number of medicinal product dosage units per one package is one of the routine risk minimisation measures. When the number of units of the prescribed medicinal product is limited, the patient is forced to contact the attending physician at shorter intervals, which increases the likelihood of monitoring his/her condition and shortens the time he spends without appropriate supervision. The release of packages for a small number of dosage units (in special cases, for one dosage unit) can also be useful if an overdose is considered one of the main risks.

Prescription Status of a Medicinal Product

315. The prescription status of a medicinal product, which introduces control over its dispensing to the public, can help reduce the risks associated with the use or misuse of such medicinal product. This can be achieved by regulating the conditions under which the medicinal product can be prescribed or the conditions under which the patient can receive it.

316. The marketing authorisation file must include details of any conditions, restrictions on the distribution or use of the medicinal product, including the conditions under which the medicinal product may become available to patients (prescription status of a medicinal product). This status includes information about whether the medicinal product is a prescription or over-the-counter medication. It may also restrict places of the medicinal product distribution (e. g., restricted dispensing procedure). Concerning medicinal products that can only be purchased with a prescription, additional conditions shall be introduced, namely, to determine which medicinal products can be purchased only with a special prescription.

Additional Risk Minimisation Measures

317. Additional risk minimisation measures shall be proposed when the introduction of such measures is necessary to ensure the safe and effective use of the medicinal product. The need to continue additional activities shall be reviewed periodically.

318. After their agreement with the Member States' authorised authority, additional risk minimisation measures become a condition for obtaining a marketing authorisation or maintaining authorisation status. Where appropriate, full information on additional risk minimisation measures shall be provided in Annex 6 to the risk management plan.

Assessing the Effectiveness of Risk Minimisation Measures

319. At the stages of updating the risk management plan, the risk minimisation plan shall include information on the assessment of impact of the implemented additional risk minimisation measures on the main

parameters that determine these measures' effectiveness. Where applicable, this information shall be provided on each of the Member States territories.

320. If applicable, the section should include a discussion of the results of any specific risk minimisation assessment performed. If a particular risk minimisation strategy is found to be ineffective or determined that the implementation of the strategy is causing an excessive burden on patients or the health system, the MA holder should consider alternative risk minimisation measures. The MA holder shall assess and comment in the risk management plan whether additional or other risk minimisation measures need to be introduced for each safety concern or, based on the assessment performed, (additional) risk minimisation measures may be excluded from the plan (e. g., when risk minimisation measures have become part of standard clinical practice). In certain cases, as a result of the assessment of the strategy, it can be concluded that risk minimisation measures cannot control the risks to the required extent to ensure the use of the medicinal product when the benefit exceeds the risk, which means the demand to withdraw the medicinal product from the market or limit its use to only that patient subgroup for which the benefits outweigh the risks.

321. If the assessment of the effectiveness of risk minimisation measures is a requirement or condition on the part of an authorised authority, these measures are included in the pharmacovigilance plan.

322. Monitoring the effectiveness of risk minimisation measures is described in Part XII of these Rules.

Risk Minimisation Plan Format

323. In this section, for each safety concern included in the safety specification, the following information on risk minimisation measures shall be provided:

a) routine risk minimisation measures, including detailed information on whether only the inclusion of relevant recommendations and information in the summary of product characteristics and package inserts is proposed, or other routine risk minimisation measures are planned;

b) additional risk minimisation measures (where necessary), including tasks for each additional activity, justification of the need and a method for assessing the effectiveness of additional risk minimisation measures.

Summary of the Risk Minimisation Plan

324. This section shall provide a table listing the routine and additional risk minimisation measures following the safety concerns identified by the safety specification (e. g., the number of the section of the Summary of Product Characteristics, which provides for routine risk minimisation measures, or a list of educational materials).

Part VI: Summary of the Risk Management Plan

325. A summary of the risk management plan for each medicinal product shall be made publicly available. The executive summary shall include the key elements of the risk management plan, with particular emphasis on risk minimisation measures. The authorised authorities shall ensure the publication of a summary of the approved risk management plans on the authorised authority’s website on the Internet.

326. The summary of the risk management plan shall be promptly updated as important changes are made to the plan. Changes to the risk management plan are assessed as important if they affect:

a) new important identified or potential risks or important changes to or deletions from the list of safety concerns;

b) the inclusion or exclusion of additional risk minimisation measures or routine risk minimisation measures implementing specific clinical measures to risk management;

c) significant changes to the pharmacovigilance plan (e. g., adding new studies to the plan or completing ongoing studies).

327. Since the summary of the risk management plan is intended for a wide audience, the information in this section shall be presented in understandable language. However, this does not mean that specialised terms should be avoided. The document shall clearly explain its purpose and its relation to other information, mainly information about the medicinal product (i. e., the summary of product characteristics, package inserts, and labeling).

328. The summary of the risk management plan must be consistent with the information provided in Modules CVII, CVIII of Part II and Parts III, IV, and V of the risk management plan and shall contain the following information:

a) the name of the medicinal product and the purposes for which its use is approved;

b) summary of safety concerns and missing information;

c) routine and additional risk minimisation measures;

d) additional pharmacovigilance activities;

Part VII: Annexes to Risk Management Plan

329. If the risk management plan applies to two or more medicinal products, the annexes are expected to apply to all products. Specific aspects that do not apply to all medicinal products in terms of risk management should be emphasised (e. g., the form for the subsequent collection of information on an adverse reaction in Annex 4 may only apply to medicinal products containing an active ingredient that has a causal link to the

reaction). The risk management plan shall contain the annexes specified below (where applicable).

Annex 1: Electronic Format of the Risk Management Plan

330. Annex 1 to the risk management plan is a structured electronic file of the risk management plan, which is not required to be submitted as part of the marketing authorisation application for the medicinal product. Annex 1 in the form of an electronic file shall be submitted in a format meeting the Requirements for the electronic applications and documents of the marketing authorisation application submitted during the marketing authorisation and expert assessment of medicinal products for medical use approved by Decision No. 79 of the Eurasian Economic Commission's Board dated June 30, 2017. This annex may be left blank.

Annex 2: Summarised Data on Planned, Ongoing and Completed Studies of the Pharmacovigilance Plan in a Tabular Form

331. This annex shall include, in tabular form, the following information on studies included in the pharmacovigilance plan (according to the current or previous version of the risk management plan, categories 1, 2, and 3 studies):

a) planned and ongoing studies, including objectives, safety concerns, and planned timing for submitting intermediate and final results;

b) studies completed, including objectives, safety concerns, and date of submission of results to authorised authorities (completed, planned submission, or indication of the reason for not submitting results).

Annex 3: Protocols of Proposed, Ongoing, and Completed Studies of the Pharmacovigilance Plan

332. Annex 3 to the risk management plan is not required to include study protocols that were not assigned by the Member State' authorised authority and were not included in the pharmacovigilance plan. This annex may include an electronic link to other modules of the electronic marketing authorisation application if these protocols and the risk management plan are submitted simultaneously with the electronic general technical document. Where the risk management plan is submitted not within the electronic marketing authorisation application, this annex shall include the protocols of studies included in the pharmacovigilance plan.

Part A of Annex 3: Requested Study Protocols of Pharmacovigilance Plan Submitted for Assessment by the Authorised Authority When Updating a Risk Management Plan Version

333. Where the requested protocols are to be submitted for consideration by an authorised authority and a MA holder plans to submit the study protocol for assessment by the authorised authority as part of the procedure for submitting a risk management plan, Part A of Annex 3 shall include this protocol. Alternatively, the study protocol can be reviewed in a separate procedure and, once agreed, should be included in Part C of this annex. The procedure for submitting the study protocol shall be agreed upon with an authorised authority.

Part B of Annex 3: Requested Changes to Previously Approved Pharmacovigilance Study Protocols Submitted for Assessment by an Authorised Authority when Updating the Risk Management Plan Version

334. If the authorised authority has requested changes to the study protocol for consideration and a MA holder plans to submit changes to the

study protocol as part of the procedure for submitting a risk management plan, Part B of Annex 3 shall include an updated protocol. Alternatively, a change to the protocol may be submitted under a separate procedure and, once agreed, shall be included in Part B of this annex. The procedure for submitting the study protocol shall be agreed upon with an authorised authority.

335. After approval by an authorised authority, the study protocols from Part A or B should be transferred to Part C of this annex with a subsequent mandatory update of the risk management plan.

Part B of Annex: 3 Approved protocols of Ongoing Studies of the Pharmacovigilance Plan and Final Research Protocols Not Submitted for the Assessment by the Authorised Authority

336. Part B of Annex 3 to the risk management plan shall include the following protocols:

a) complete protocols that have previously been assessed by the authorised authority and agreed upon (i. e., no re-submission of the protocol has been requested). The protocol shall be attached with a document indicating the name of the procedure under which the protocol was approved and the conclusion date. The indicated procedure mane may include an electronic reference or a link to other modules of the marketing authorisation application if the protocols were previously submitted as part of this marketing authorisation application;

b) final protocols for other Category 3 studies: Protocols that have not been requested for review by the authorised authority and are provided by the MA holder for information only.

337. Completed study protocols should be excluded from this annex after the final study reports are submitted to the authorised authority for evaluation.

Annex 4: Special Forms for Subsequent Collection of Information about Adverse Reactions

338. This annex shall include all forms for the subsequent collection of information on adverse reactions used by the MA holder to collect additional data on specific safety concerns. The use of the forms for the subsequent collection of information included in this annex shall be detailed in the pharmacovigilance plan of risk management plan as a component of routine pharmacovigilance activities.

339. The forms of the subsequent data collection to be included in this annex may also be referred to as questionnaires for additional adverse reaction data, adverse reaction data collection form, or form for the subsequent collection of adverse reaction data.

Annex 5: Protocols of Proposed and Ongoing Studies Included in Part IV of the Risk Management Plan

340. This annex shall include links or references to other parts of the electronic marketing authorisation application, provided that the efficacy study protocol is included in the electronic common technical document or to the protocol for the assigned efficacy study included in Part IV of the risk management plan.

Annex 6: Detailed Information on Proposed Additional Risk Minimisation Measures

341. Where applicable, this annex shall contain proposed and agreed upon (where applicable) projects with the key information on additional risk mitigation measures.

Annex 7 Other Supporting Data (Including References)

342. Where applicable, to avoid duplication of references, this annex shall include references to electronic marketing authorisation application or links to other documents included in other modules of the marketing authorisation application.

Annex 8 Review of Changes Made to the Risk Management Plan

343. This annex shall provide a chronological listing of all significant changes to the risk management plan. The information shall include a summary of the changes, the date and version number of the risk management plan for all of the following changes:

a) adding, removing, or changing the classification of safety concerns;

b) adding or removing the studies from the pharmacovigilance plan;

c) changing activities in the risk management plan in terms of measures suggesting certain clinical actions to manage risks or additional risk minimisation measures.

Annex 9: Information on the Differences between the Risk Management Plans in the Member States and the Current Risk Management Plan Version

344. This annex is submitted in case information in the sections of the risk management plan in the Member States differs from the information in the corresponding sections of the current risk management plan version. A

description of these differences is presented following the data format and structure requirements.

7. Relationship Between the Risk Management Plan and the Periodic Safety Update Report

345. The main post-authorisation pharmacovigilance documents are a risk management plan and a periodic safety update report. The periodic safety update report's main objective is a retrospective integrated post-authorisation risk–benefit assessment; while the risk management plan's objective is prospective pre-authorisation and post-authorisation risk–benefit ratio management and planning. Thus, these documents are complementary.

346. If the periodic safety update report and the risk management plan are submitted simultaneously, the plan should reflect the conclusion on the safety and efficacy profile made in the periodic safety update report. For example, if the periodic safety update concludes that a new signal has been identified and is classified as an important identified or important potential risk, that important risk should be included as a safety concern in the updated version of the risk management plan submitted simultaneously with the periodic safety update report. The pharmacovigilance plan and risk minimisation plan shall, in this case, be updated accordingly to reflect the MA holder's proposals for further study of this safety concern and measures to minimize the associated risk.

347. The information shall be consistent, but may differ in format in the following sections of the periodic safety update report and risk management plan:

a) module CIII: Clinical Exposure Trial of Part II of the risk management plan and Subsection 5.1 Total Number of Patients Exposed to the Medicinal Product in Clinical Trials of the periodic safety update report;

b) Module CV Post-authorisation Stage of Part II of the risk management plan and Subsection 5.2 Total Number of Patients Exposed to the Medicinal Product According to the Data on its Use in the Market of the periodic safety update report;

c) Module CVII Identified and Potential Risks of Part II of the risk management plan and Subsection 16.1 Summarizing Information on Safety Concerns of the periodic safety update report, Module CVIII Summary of Safety Concerns of Part II of the risk management plan and Subsection 16.4 Risk Characteristics of the periodic safety update report;

d) Section Assessment of the Risk Minimisation Measures' Effectiveness of Part V of the risk management plan and Subsection 16.5 Risk Minimisation Measures' Effectiveness of the periodic safety update report.

8. Quality Systems and Records Management

348. Although many experts may be involved in writing a risk management plan, the entire responsibility for its quality, accuracy, and scientific integrity rests with the MA holder. The MA holder is responsible for updating the risk management plan when new information becomes available and must apply the quality assurance principles set out in Section II of these Rules. The MA holder shall ensure control and documentation of the procedure for submitting the risk management plan to the authorised authority, indicating the dates of submission and all significant changes made to each version of the risk management plan. These records, the risk management plan, and any documents related to the information within the specified plan may be audited and inspected by pharmacovigilance inspectors.

9. Requirements for the Risk Management Plan Submission

Requirements for Submitting a Risk Management Plan by MA Holders when Applying for the Medicinal Product Marketing Authorisation and Bringing into Line with the Union’s Requirements

349. When applying for a marketing authorisation of a medicinal product and bringing the marketing authorisation application for a medicinal product in line with the Union’s requirements, it is necessary to submit a risk management plan with a description of the risk management system and the plan summary for all medicinal products, except for the cases specified in paragraph 350 of these Rules.

Where the risk management plan is submitted as part of the marketing authorisation application, its form and language shall comply with the requirements of the Rules for Marketing Authorisation and Expert Assessment.

350. When applying for bringing the marketing authorisation application for a medicinal product in line with the Union’s requirements, it is not required to submit the risk management plan with a description of the risk management system and the plan summary for:

a) the medicinal product, whose active ingredient has been well studied during medical use; in contrast, its efficacy and an acceptable degree of safety have been recognised, and at least 10 years have passed since the date of the first systematic and documented use of the active ingredient(s) of this medicinal product in a Member State, which assesses whether the application is brought in line with the Union’s requirements and which has no risk management plan at the time of bringing the marketing authorisation application into compliance with the Union’s requirements;

b) herbal medicinal product, which meets the criteria for submitting a simplified marketing authorisation application;

c) a homeopathic medicinal product that meets the criteria for submitting a simplified marketing authorisation application.

351. The exceptions specified in paragraph 350 of these Rules, do not apply and a risk management plan for the indicated groups of medicinal products shall be submitted in the following cases:

a) where a new therapeutic indication is introduced in the general characteristics of the medicinal product and the package insert;

b) where a safety concern emerges, affecting the risk–benefit;

c) where ensuring the medicinal product use when the benefit exceeds the risk requires introducing some additional pharmacovigilance measures or additional risk minimisation measures.

352. At the post-authorisation period, it may be required to submit an update to the risk management plan or a new risk management plan at any time during a medicinal product's life cycle in the following cases:

a) at the authorised authority's request in the event of a safety concern affecting the risk–benefit ratio;

b) when making changes to the current marketing authorisation application accompanied by a change in the list of safety concerns, the emergence of new additional measures for pharmacovigilance, or the need to make changes to risk minimisation measures. Submission of the risk management plan update may be required in cases of changes in indications, introducing a new dosage form, a new administration route, and changes in biotechnological products' manufacturing process.

Requirements in Special Situations

353. Applying for marketing authorisation of a medicinal product with the complete content of Modules 1–5 of the marketing authorisation application, it is necessary to submit all parts of the risk management plan. In

all other cases of applying for the marketing authorisation of a medicinal product, the requirements for the content of the risk management plan are determined based on the principle of proportionality to the identified and potential risks of a medicinal product and the need to obtain safety data at the post-authorisation period, in connection with which some parts or modules may be omitted if only the Member State’s authorised authority does not provide other requirements. The minimum reporting requirements for the parts of the risk management plan are shown in Table 2.

Table 2

List of parts of the risk management plan when applying for the marketing authorisation of a medicinal product for different types of medicinal products

Medicinal Product Type	Risk management plan													
		Part II												
	Part I:	CI module	Module CII	Module CIII	Module CIV	Module CV	Module CVI	Module CVII	Module CVIII	Part III	Part IV	Part V	Part VI	Part VII
Submission of the full content of Modules 1 to 5 of the marketing authorisation application	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Generic medicinal product	+							‡	+	+	*	#	+	+
Hybrid medicinal product	+	†		†				†	+	+	+	#	+	+
Fixed combination medicinal products—with a new active ingredient in the composition	+	§	§	§	§	§	§	+	+	+	+	+	+	+
Fixed combination medicinal product—no new active ingredient in the composition	+		†	†				‡	+	+	*	#	+	+
Well-established use medicinal product	+							+	+	+	+	+	+	+
Biosimilar medicinal product	+		+	+	+	+	+	+	+	+	+	+	+	+

Notes:

1. The “+” symbol means that this section’s information is presented to the full extent of the requirements.
2. The “‡” symbol means that this section’s information is provided if the reference medicinal product does not have an approved risk management plan and the summary of the risk management plan is not published on the website of the Member State’s authorised authority.
3. The “*****” symbol means that this section’s information is provided if post-authorisation efficacy studies are assigned to the reference medicinal product.
4. The “#” symbol means that this section may indicate the safety information’s compliance in the summary of product characteristics and the package inserts.
5. The “†” symbol means that this section’s information requirements are based on the principle of proportionality to the associated risks, taking into account the new safety data obtained, as well as possible differences from the reference medicinal product.
6. The “§” symbol means that the information in this section shall be presented with a more detailed description and assessment as regards a new active ingredient to a new active ingredient.

Applying for Marketing Authorisation of a Generic Medicinal Product

354. When applying for marketing authorisation of a generic medicinal product, the information in the risk management plan shall meet the following requirements:

a) in Part I of the risk management plan, the information requirements correspond to the requirements for applying for marketing authorisation of a medicinal product with the full content of Modules 1–5 of the marketing authorisation application;

b) in Part II of the risk management plan, the information shall be presented subject to the following possible conditions:

the reference medicinal product has a risk management plan. In this case, Modules CI–CVII of the risk management plan may not be submitted. Module CVIII shall include summarised safety information generated from the summarised safety information for the reference product. If, in the opinion of a MA holder, there is sufficient evidence to exclude from the list or change the list of safety concerns contained in the risk management plan of the reference product, Module CVII shall include a detailed justification of the existing grounds for making such changes. Likewise, if the MA holder has identified a new safety concern related to a generic medicinal product (e. g., risks associated with a new excipient or a new safety concern arising from any clinical data obtained), detailed information and justification for this difference with a detailed description of the new safety concern shall also be mentioned in Module CVII;

the reference medicinal product does not have a risk management plan; still, an updated list of safety concerns for the active ingredient(s) of the product is published on the authorised authority’s website in the Internet. In this case, when developing the safety specification, requirements similar to

the requirements for medicinal products that have a risk management plan of the above paragraph are met. If more than one list of safety concerns is published on authorised authority's the website in the Internet for a given active ingredient(s), the MA holder shall justify the choice made in Module CVIII;

The reference medicinal product does not have a risk management plan and the list of safety concerns for the active ingredient(s) of the medicinal product is not published on the authorised authority's website in the Internet. In this case, the safety specification includes complete information on Modules CVII and CVIII. Module CVII shall provide a critical assessment of the available information on the risks associated with the use of the medicinal product (e. g., data from preclinical and clinical trials, scientific medicine literature, information from the developer of the reference medicinal product) and a list of important identified and potential risks, as well as important missing information;

c) in Part III of the risk management plan, the information shall include a description of pharmacovigilance activities in accordance with the requirements established by paragraphs 287–305 of these Rules.

The MA holder of the generic medicinal product needs to participate in planned or ongoing studies conducted by the MA holder for the reference product in cases where it is important to collect available or prospective data within one study. For example, obtaining data on certain safety aspects of a new medicinal product necessary further to characterize the safety profile of an active ingredient may require the inclusion of patients in separate studies with the same or similar objectives (e. g., registries of pregnant women, registries of patients with certain diseases, all post-authorisation safety studies, aimed at assessing the results of long-term use), which creates an

unreasonable burden on patients, doctors and researchers and shall be optimised through joint studies.

The authorised authority, where applicable, may also consider the prescription of studies to be carried out regarding a generic medicinal product;

d) Part IV of the risk management plan may be left blank if a post-authorisation efficacy study was not ordered for a generic medicinal product;

e) in Part V of the risk management plan, where no additional risk minimisation measures are taken for the reference medicinal product, it is sufficient to state that the safety information in the summary of product characteristics and package inserts of the generic medicinal product complies with the safety information in the summary of product characteristics and the package inserts of the reference medicinal product. If new (other) risks arising from the use of a generic medicinal product are identified, measures shall be proposed to minimize the risks for relevant safety concerns in accordance with the requirements established for this section (Section V) when applying for marketing authorisation of a medicinal product with the entire content of Modules 1–5 of the marketing authorisation application.

If any additional risk minimisation measures are taken in relation to the reference medicinal product, full information on the section is required for the generic medicinal product in accordance with the requirements established in paragraphs 307–324 of these Rules;

f) the information in Part VI of the risk management plan shall comply with the requirements established when applying for marketing authorisation of a medicinal product with the full content of Modules 1–5 of the marketing authorisation application and be presented in the volume determined by the above requirements for sections of the risk management plan for a generic medicinal product in accordance with paragraphs 325–328 of the Rules;

g) the information in Part VII of the risk management plan shall comply with the requirements established when applying for marketing authorisation of a medicinal product with the entire content of Modules 1–5 of the marketing authorisation application. In terms of Annexes 4 and 5 to the risk management plan, the MA holder of the generic medicinal product should use the materials, the content of which has been brought in line with similar materials of the reference product.

Applying for a Marketing Authorisation of a Hybrid Medicinal Product

355. The information requirements in the risk management plan for a hybrid medicinal product is aligned with the requirements for a generic medicinal product in paragraph 354 of these Rules.

In Module CVII of Part II the risk management plan, the MA holder shall provide a detailed assessment of the differences in the hybrid medicinal product compared with the reference medicinal product, for example, the active ingredient, indications, strength, dosage form or route of administration, with a justification for the possibility of using a list of safety concerns of the reference product, or the need for changes (inclusion of additional or exclusion of safety concerns from the current list), resulting from these differences. Clinical trial data that make grounds for applying for marketing authorisation shall be included in Modules CI and CIII of Part II of the risk management plan. Other parts of the risk management plan shall also be brought in accordance with this information (e. g., Parts V and VI of the risk management plan).

Applying for Marketing Authorisation of a Fixed Combination Medicinal Product

356. The information requirements in the risk management plan when applying for marketing authorisation of fixed combination medicinal products are determined based on the following conditions:

for a fixed combination medicinal product with a new active ingredient, the information shall comply with the requirements established for applying for marketing authorisation of a medicinal product with the entire content of Modules 1–5 of the marketing authorisation application in accordance with paragraph 353 of these Rules. The information in the Modules –CI to CVI of the risk management plan shall be presented with an emphasis on the new active ingredient;

for a fixed combination medicinal product that does not contain a new active ingredient, the information shall comply with the requirements established for a generic medicinal product. Concerning the requirements of Part II of the risk management plan, "reference product" should be understood as "any or all authorised medicinal products containing similar active ingredients included in this fixed combination."

New information obtained from the fixed combination study shall be presented in Modules CII and CIII of Part II of the risk management plan.

Applying for the Marketing Authorisation of a Well-Established Medicinal Product

357. When applying for the marketing authorisation of a well-established medicinal product, information in the risk management plan shall meet the following requirements:

a) in Part I of the risk management plan, the information requirements correspond to the requirements for applying for marketing authorisation of a

medicinal product with the full content of Modules 1–5 of the marketing authorisation application;

b) in part II of the risk management plan, information is presented in Modules CVII and CVIII. The MA holder shall provide a justification for the proposed safety concerns or a justification for the absence of safety concerns based on the available data published in the scientific medical literature;

c) in Parts III and IV of the risk management plan, the information requirements correspond to the requirements for applying for marketing authorisation of a medicinal product with the full content of Modules 1–5 of the marketing authorisation application.

Applying for the Marketing Authorisation of a Biological Medicinal Product

358. When applying for the marketing authorisation of a biological medicinal product, a risk management plan shall be developed with due account for the following requirements:

a) reflection of assessment of the specific immunogenicity risk with possible clinical consequences and the risk of infectious agent transmission.

b) ensuring the implementation in the pharmacovigilance plan of routine and additional measures to trace the name and batch of a biological medicinal product during the use and detection of adverse reactions, assess the base frequency of adverse events of special interest, and continuous monitoring of the frequency of suspected adverse events of special interest at the stage of post-authorisation use to the detection of the excess of the expected frequency, and measures to study specific risks at the post-authorisation stage (e. g., immunogenicity);

c) ensuring the inclusion in risk minimisation measures of actions aimed to trace a biological medicinal product's name and batch during use and detecting adverse reactions.

Applying for Authorisation of a Homeopathic Medicinal Product and Herbal Medicinal Product, which do not Meet the Criteria for Submitting a Simplified Marketing Authorisation Application

359. When applying for marketing authorisation of a homeopathic medicinal product and herbal medicinal product that do not meet the criteria for submitting a simplified marketing authorisation application, the information requirements are determined based on the type of application for marketing authorisation.

Requirements for the First Submission of the Risk Management Plan after Marketing Authorisation of the Medicinal Product

Submitting New Risk Management Plans at the Request of the Member States' Authorised Authority Due to an Identified Safety Concern

360. Requirements for the information in the risk management plan submitted at the request of an authorised authority in connection with the identified safety concern comply with the requirements established for generics in the absence of a risk management plan for the reference product.

361. The Member State's authorised authority may determine the requirement for a MA holder to submit in Section CVII of the safety specification regarding the identified safety concern or provide complete information on safety concerns about the medicinal product. The authorised authority makes this decision with the determination of the most optimal option in the current circumstances.

Voluntary Submission of New Risk Management Plans after Marketing Authorisation of the Medicinal Product

362. Where the MA holder voluntarily submits a risk management plan after marketing authorisation of the medicinal product, the requirements for information in the risk management plan are determined according to the type of marketing authorisation of the medicinal product during the initial application for the marketing authorisation of the medicinal product (e. g., marketing authorisation of a medicinal product with the submission of the entire content of Modules 1–5 of the marketing authorisation application, marketing authorisation of a generic medicinal product, etc.) and in compliance with the requirements established by paragraph 353 of these Rules.

Submitting a Risk Management Plan to the Member States' Authorised Authorities

363. When initially applying for marketing authorisation, the risk management plan shall be submitted as part of the marketing authorisation application. When submitting a risk management plan as part of an electronic marketing authorisation application, the document is formed as PDF files or in another electronic format determined by the authorised authority's requirements for the electronic format of documents included in the marketing authorisation application of a medicinal product in accordance with the marketing authorisation procedure being performed. The risk management plan is submitted to the Member State's authorised authority in the language established by the requirements of the Rules for Marketing Authorisation and Expert Assessment.

10. Risk Management Plan Updates

364. If a MA holder has previously submitted the risk management plan during the procedure for the marketing authorisation of a medicinal product for an active ingredient, any subsequent submissions shall be provided as an update unless otherwise specified. Each submission of the risk management plan shall be versioned and dated. This refers to submitting the risk management plan in its entirety or only to a part or module of it.

365. An update of the risk management plan is submitted when changes are made to the list of safety concerns when new or significant changes are introduced in additional pharmacovigilance activities included in the plan or additional risk minimisation measures. Significant changes to approved pharmacovigilance additional activities may be due, for example, to changes in the study's objectives, the target population, or the agreed reporting dates for the study results. Significant changes in additional risk minimisation measures may be associated, for example, with the addition of educational materials with a new safety concern, which is also reflected in other relevant sections of the risk management plan. Significant changes in additional pharmacovigilance activities or additional risk minimisation measures also cover excluding these additional measures from the risk management plan.

366. An update of the risk management plan may be required in cases where the assessment of the data obtained determines the need to complement the routine pharmacovigilance activities performed with other types of routine activities, in addition to actions on adverse reactions and signal management.

In terms of changes in routine risk minimisation activities, an update of the risk management plan may be required when supplementing the recommendations with certain special clinical risk management measures (e.

g., updating the risk management plan may also be justified in case of significant changes in the plan for annual extended safety monitoring (routine pharmacovigilance activities) or when an additional component of routine monitoring is included (e. g., regular monitoring of kidney function) as a recommendation in Subsection 4.4 of Section 4 of the summary of medicinal product characteristics. The need to update the plan for assessing the effectiveness of risk minimisation measures shall also be considered when updating the risk management plan.

367. An update to the risk management plan may be required upon completing an emerging safety issue assessment and confirmation of the new safety concern as an important identified or potential risk with the need to make changes to the safety concern list.

368. Unless otherwise specified by the requirements, a document displaying in tabular form (“before–now”) the changes made in the last update of the risk management plan (where applicable) and changes compared to the current approved version of the risk management plan shall be included in each submitted risk management plan update.

369. A medicinal product can have only one currently approved version of the risk management plan. If there are differences in the information in the risk management plan (e. g., in terms of epidemiology, the stage of implementation of additional risk minimisation measures, assessment of the risk minimisation measures’ effectiveness) in the Member States, a description of these differences may be presented in Annex 9 to the risk management plan in accordance with the requirements for the format and structure of the data presented in the data risk management plan. If multiple updates to the risk management plan are submitted during the procedure, the latest version submitted will be considered the currently approved risk management plan for subsequent updates and tracking changes.

370. If an update of the risk management plan is submitted as part of the procedure, the risk management plan is considered approved at the end of the procedure if all changes are evaluated as acceptable.

371. At the post-authorisation stage, the submission procedure for a new or updated risk management plan is carried out in cases and in accordance with the procedure for making changes to the marketing authorisation application of a medicinal product established by Annexes 19 and 20 to the Rules for Marketing Authorisation and Expert Assessment, except for the cases when a new or updated risk management plan is submitted as part of performing other obligations imposed by the authorised authority.

11. Managing the Risk Management Plan when Performing Parallel Procedures

372. If two or more procedures are simultaneously performed for a medicinal product that require submitting a risk management plan, a single combined risk management plan should be submitted with the appropriate division of data in Module CIII of Part II of this plan. The best option for submitting an update of the risk management plan in the event of several regulatory procedures that potentially affect the risk management plan's content shall be discussed with an authorised authority before submitting the document.

12. Updating the Risk Management Plan when Preparing a Periodic Safety Update Report

373. If, when preparing a periodic safety update report, the necessary to make changes to the risk management plan arises as a result of identifying new safety concerns or other data provided in the periodic safety update

report, it is necessary to submit the updated risk management plan to the Member State's authorised authority simultaneously with submitting a periodic safety update report. In this case, it is not required to submit the updated risk management plan under a separate procedure. Where the time frame for submitting both documents coincides, but the changes are not related to each other; in that case, the risk management plan submission shall be considered an independent amendment and submission to an authorised authority of an updated version of the document.

13. Risk Management Plan Assessment by the Authorised Authorities

374. With regard to the medicinal products registered in accordance with the Member States' legislation, the authorised authorities are responsible for assessing the risk management plan and arranging expert work on the risk management plan assessment on a uniform basis.

375. The Member State's authorised authority may oblige a MA holder to monitor the risk management system for each medicinal product in case of concerns about risks affecting the risk–benefit ratio, and also provide a detailed description of the risk management system that the MA holder plans to implement for the corresponding medicinal product.

376. For medicinal products authorised under a decentralised procedure or recognition procedure, the risk minimisation plan includes risk minimisation measures recommended by a reference Member State's authorised authority and subsequently agreed by the authorised authority of the Member State concerned. Additional risk minimisation measures and other conditions or restrictions aimed at ensuring the use of a medicinal product when the benefit outweighs the risk are conditions for granting a marketing authorisation.

377. Where changes occur in relation to the risk minimisation plan of the reference medicinal product or a decision is made to change the risk minimisation measures for this active ingredient(s), the Member State's authorised authority shall ensure that the holder of the marketing authorisation certificate for medicinal products containing the same active ingredient(s) makes timely changes in risk minimisation measures.

14. Transparency of the Risk Management Plan Assessment

378. The Member States' authorised authorities shall ensure the mutual availability of reports on the assessment results of the submitted risk management plans and a summary of the risk management plans through the integrated information system of the Union.

379. The authorised authority shall provide public access to the summary of approved risk management plans on its website on the Internet. For these purposes, the MA holder additionally submits to the authorised authority a summary of the risk management plan in the form of a separate electronic document.

VII. Arranging Work with Information on Adverse Reactions

380. This section sets out the basic principles for data collection, data management, and individual reporting of suspected adverse reactions associated with the use of medicinal products authorised in the Member States.

381. This section does not define the requirements for individual reporting of events or aspects of using a medicinal product not leading to the development of adverse reactions (e. g., cases of overdose, misuse, or medication errors, not accompanied by the development of adverse clinical

symptoms). This information shall be collected, analysed, and presented in a periodic safety update report to interpret available safety data or assess the risk–benefit ratio.

1. Collection of Adverse Reaction Reports

382. Authorised authorities and marketing authorisation holders should collect and organize solicited and unsolicited reports of suspected adverse reactions received from various sources.

383. To ensure the possibility of collecting a sufficient number of adverse reaction reports and subsequent scientifically-based assessments, it is necessary to develop the pharmacovigilance system.

384. The pharmacovigilance system shall be designed to provide an adequate assessment of the quality of the collected adverse reaction reports (in terms of authenticity, legibility, accuracy, consistency), the maximum completeness of clinical data assessment and the ability to perform validation.

385. Handling of data contained in reports of adverse reactions shall be arranged with due account for the Member State’s legislation on personal data protection.

386. The pharmacovigilance system should be structured to allow for the timely validation of reports of suspected adverse reactions and their exchange with the authorised authorities and MA holders within the time limits established by the legislation of the Member States.

387. Reports with safety information of a medicinal product collected at the post-authorisation use stage may be divided into two types: solicited and unsolicited reports.

Unsolicited Adverse Reaction Reports

Spontaneous Reports

388. Spontaneous report is sent by a health system professional, patient or consumer to the authorised authority, MA holder or other organisation (e. g., to the regional pharmacovigilance center, toxicological center) without any prior request. A spontaneous report describes one or more suspected adverse reactions in a patient treated with a medicinal product.

389. Spontaneous reporting does not include reports received in the course of study or other organised data collection types. Spontaneous reports include the following reports of suspected adverse reactions:

a) adverse reaction reports submitted in response to promotion measures in the form of direct reporting to health professionals, press releases, interviews of health professionals by MA holders, information sharing of patient organisations with their members or pharmaceutical class action lawsuits;

b) unsolicited reports sent by consumers regardless of their subsequent medical confirmation;

c) reports that are not associated with any of the organised data collection methods and received through the medicinal product information reporting system or result from the distribution of product information or educational materials;

d) messages found on the Internet or digital media;

e) individual reports received from multiple reporters, with at least one sent without prior request;

f) reports received during a non-interventional post-authorisation study for which the study protocol did not determine a systematic data collection;

g) reports resulting from compassionate use of unauthorised medicinal products prescribed in exceptional circumstances as compassionate provision or within personalised programs for the use of unauthorised medicinal products if these programs did not determine the systematic collection of adverse reaction data.

390. The primary source of the suspected adverse reaction is the person who reported the adverse reaction. If the information about one adverse reaction comes from several primary sources, including from a healthcare professional, patient, or consumer, data from all primary sources shall be included in the "Source" section of the adverse reaction report form.

391. A consumer-submitted adverse reaction report is considered clinically validated if a healthcare professional subsequently confirms the development of the adverse reaction in the patient. The consumer's clinical confirmation of an adverse reaction report includes the presence of data from the patient's medical records (e. g., laboratory or other data) in the report that confirms the patient's development of an adverse reaction and the presence of an identifiable healthcare professional that suggests a relationship between taking the product and the development of an adverse reaction. Where a report of an adverse reaction was sent by a consumer, being a person with a medical education, this report is also assessed as having medical evidence.

392. In case of receiving a spontaneous report about the development of an adverse event, in which there is no indication of the presence of a causal link, this adverse event is considered as an adverse reaction. Therefore, all spontaneous reports submitted by healthcare professionals, patients, or consumers are considered suspected adverse reactions on the basis that their presentation contains the reporter's assumption about a relationship between an adverse event and a suspected medicinal product. An exception is reports in which the reporter indicates of the absence of such relationship.

Adverse Reaction Reports Published in the Scientific Medical Literature

393. The medical literature is an important source of information for monitoring the safety profile and the risk–benefit ratio of medicinal products, especially concerning the discovery of new safety signals or emerging safety issues.

394. MA holders should conduct a systematic, at least once a week, review of the scientific medical literature in widely used reference databases (including the bibliographic database of articles in the medical sciences (Medline) or the biomedical and pharmacological bibliographic database of published literature intended to support information managers and pharmacovigilance in accordance with the regulatory requirements for a registered medicinal product (Embase)). The MA holder should ensure that the scientific medical literature review includes looking through the databases containing the maximum number of references to articles related to the monitored medicinal product. Besides, it should be ensured that all company representatives of the MA holder are aware of local medical publications and inform the MA holder's safety department accordingly.

395. MA holders should review the reports of suspected adverse reactions published in the scientific medical literature, including in conference proceedings or draft monographs, to identify and record such reports as spontaneous reports or reports identified in the course of non-interventional post-authorisation studies.

396. If more than one medicinal product is mentioned in the publication, then the relevant MA holder should consider products identified by the authors of the publication as having at least a possible causal link with the identified suspected adverse reactions.

397. Reports evaluated as valid shall be submitted to the Member States' authorised authorities in accordance with the requirements of these Rules. The starting time for submitting an adverse reaction report is determined from the moment when the MA holder obtained information about an adverse reaction that meets the minimum required information requirements for urgent reporting. One adverse reaction case should be recorded for each identifiable reported patient, and the report should include important medical information for the assessment. The first author of the publication is considered the primary source of the adverse reaction report; data concerning the publication's co-authors do not need to be documented in the primary sources of information.

Adverse reaction reports from Other Sources

398. If a MA holder becomes aware of a suspected adverse reaction report from a non-medical source, such as non-core or other media, he/she should handle it according to the approaches recommended for spontaneous reports. Such a case should be worked through to obtain the minimum required information that constitutes a valid adverse reaction report. The submission time frame for this type of report is the same as for all spontaneous messages.

Information about Suspected Adverse Reactions Received from the Internet Network or Digital Media

399. MA holders should regularly browse the Internet or digital media (e. g., websites, web pages, blogs, video blogs, social networks, Internet forums, video chats, health portals) under their control or responsibility for potential suspected adverse reaction reports. In this context, digital media are considered sponsored by an MA holder if the MA holder owns, pays for, or

controls them (and a donation (financial or otherwise) to a telecommunications organisation or website by a drug manufacturer or the MA holder is not ownership, provided that the manufacturer or the MA holder has no control over the final information content of the site). The frequency of reviewing these sources should be such that the time requirement for submitting potential valid adverse reactions to the Member States' authorised authorities is met, commencing the date the information was posted. MA holders should use their own websites to optimize the collection of suspected adverse reaction information.

400. Information on cases of suspected adverse reactions reported on the Internet or digital media received without request should be handled as unsolicited reports with reporting time requirements applied, as for all spontaneous reports.

401. In the case of adverse reactions reported on the Internet or digital media, the identity of the reporter refers to the verification of the existence of a real person, that is, the ability to verify the correctness of the reporter's contact details (e. g., a valid email address was provided). Contact information should only be used for pharmacovigilance purposes. Where no information about the country of the primary source is available, then it should be the country where the information was obtained or where monitoring is carried out.

402. If the MA holder becomes aware of a suspected adverse reaction reported in digital media that the MA holder does not sponsor, the report should be evaluated to determine if it is suitable for urgent reporting.

Solicited Adverse Reaction Reports

403. Solicited reports of suspected adverse reactions are received from organised data collection systems that include clinical trials, non-

interventional trials, registries, personalised programs of the use of unauthorised products, other programs of the use of such products prescribed in exceptional circumstances as compassionate provision (use of a medicinal product for incurable or untreatable diseases, etc.) and disease monitoring, interviewing patients or healthcare professionals or collecting data on the medicinal product efficacy or patient's adherence.

404. Suspected adverse reaction reports received from any of these data collection systems should not be considered spontaneous reports except in the following cases:

a) reports of suspected adverse reactions received during a non-interventional post-authorisation study for which the study protocol did not determine a systematic data collection;

b) reports of suspected adverse reactions received as a result of compassionate use of unauthorised medicinal products or personalised programs for the use of unauthorised medicinal products if these programs did not determine the systematic collection of adverse reaction data.

405. As part of the reporting procedure, solicited reports of suspected adverse reactions should be classified as investigational reports, and validation and causal link assessment should be performed to ensure that they meet urgent reporting conditions.

406. Requirements for the organisation of work with solicited adverse reaction reports are established in paragraph 466 of these Rules.

2. Report Validation

407. Only individual case safety reports that have positive validation results are subject to urgent reporting. All adverse reaction reports before submitting to the Member States' authorised authorities shall be validated for

the minimum information required to fulfill this requirement. The minimum information required includes:

a) information on one or more identifiable reporter (primary source) who can be identified by attributes such as qualifications (e. g., doctor, pharmacist, pharmacist, another healthcare professional, patient, consumer, or other non-medical person), name, initials, or location (address) (e. g., the name of the reporter's organisation, street, city, state, postal code, country, email, telephone number). When working with the reporters' personal data, one shall comply with the relevant Member States' legislation on personal data protection.

A reporter is considered identifiable if the organisation which sent an adverse reaction report has some reliable data to confirm existence of the reporter who submitted information about the development of an adverse reaction based on available data. It should be ensured that all parties submitting information about an adverse reaction are identified, including additional information upon request. It is necessary to use the available opportunities to obtain the reporter's contact information to enable the subsequent collection of adverse reaction data. If the reporter is unwilling to provide contact details, the adverse reaction report should be considered valid, provided that the organisation informed of the adverse reaction case can prove it directly with the reporter.

An individual case safety report will not be considered valid for submission to an authorised authority unless it contains the information for identification of data on qualifications, country of location or other data of at least one reporter. In the absence of data on the reporter's qualifications, the report by default is considered to be received from a consumer. To enable follow-up monitoring of duplicate reports, it is required to indicate all reporters (not just the primary source) (where applicable) in individual case

safety reports. Information about an adverse reaction received from third parties, not in direct contact with the patient is not considered a valid adverse reaction report unless confirmed directly by the patient, the patient's physician, or a reporter in direct contact with the patient;

b) information about the identified patient. To identify a patient, at least one of the following characteristics is allowed: the patient's initials, medical record number (outpatient, inpatient records, cards with examination results), date of birth, age or age group, gestational age and gender. However, a patient is considered identifiable if, based on the available data, it is possible to confirm the patient's existence. Therefore, patient identification information shall be as complete as possible, subject to the Member State's legislation on personal data protection. A report can be considered valid for subsequent submission to the authorised authority if at least one of the above patient's characteristics is available. A report indicating several patients is not considered valid if there is no information on at least one of the patient's above individual characteristics to generate a valid adverse reaction report;

c) information on one or more suspected medicinal product or active ingredient. Interacting medicinal products pertain to suspected medicinal products;

d) details of one or more suspected adverse reactions. If the primary source makes an explicit statement that a causal link between the prescription of the medicinal product and the adverse reaction is excluded, and the recipient (the authorised authority or a MA holder) agrees, the report is defined as an invalid adverse reaction report, as this means no suspected adverse reaction. A report is also defined as an invalid individual case safety report if it is informed that the patient has experienced an adverse reaction but no indication of the type of this reaction or a description of the experienced reaction is provided. Similarly, an individual case safety report is

defined as invalid if it contains information only about the outcome and subsequent data collection does not provide any possibility to obtain a clinical justification for identifying an adverse drug reaction as the cause of the resulting outcome, or the primary source does not indicate availability of at least a possible relationship with the product administration. For example, when receiving information about the sudden death of a patient undergoing treatment in a hospital, it is necessary to supplement the report with a clinical assessment justifying the definition of this condition as an outcome of an adverse reaction or referring to the number of adverse events. When assessing sudden death in a patient receiving prescription drug therapy, the assumption should be made that there is a relationship between the outcome and treatment. When classified as valid, adverse reaction reports are subject to immediate reporting.

408. When collecting suspected adverse reaction reports via the Internet or digital media, the term “identifiable” refers to the ability to verify the existence of the reporter (source) and the patient.

409. Absence of any information specified in paragraph 407 of these Rules means that the case is considered incomplete and is not subject to the procedure for urgent reporting of adverse reactions. The authorised authorities and MA holders shall be cautious in collecting missing data in reports; actions for the subsequent data collection of adverse reaction reports shall be documented. However, reports of adverse reactions the minimal in which information is incomplete should be recorded within the pharmacovigilance system for use in ongoing safety assessment activities.

Upon receipt of the minimum data missing in reports of an adverse reaction (including a review of the relationship of an adverse reaction with a medicinal product administration), the individual report of an adverse

reaction is assessed as valid and is subject to reporting in accordance with the requirements of these Rules.

410. If one party (an authorised authority or MA holder) becomes aware that a reporter may have reported a suspected adverse reaction to another interested party, such a report should nevertheless be considered a valid adverse reaction report and included in the submission of individual case safety reports. An adverse reaction report shall include all the important information necessary to detect a duplicate report.

411. Where there is a disagreement between an investigator and a MA holder or study sponsor in assessing the causal link between the administration of a suspected medicinal product and the development of an adverse reaction during post-authorisation non-interventional studies, the case of an adverse reaction should not be relegated to a lower reliability category. An individual adverse reaction reports should include the views of the investigator and MA holder or study sponsor.

412. A valid consumer adverse reaction report should not be categorised as a non-drug-related adverse event unless the relationship is confirmed by a healthcare professional indicated by the consumer for subsequent information sharing. An individual case safety report should reflect the consumer and the healthcare professional’s opinions regarding assessing the relationship by different primary sources.

413. Where there is a disagreement between a reporter and a MA holder or the authorised authority on assessing the adverse reaction as serious, the adverse reaction seriousness should not be downgraded.

3. Follow-Up Work with Adverse Reaction Reports

414. Where the initial receipt of a suspected adverse reaction report contains incomplete information, some follow-up work should be carried out

to obtain additional detailed information, besides that minimum required, which is essential for the scientific evaluation of cases of adverse reaction development. This work is important for monitored events of special interest, cases of medicinal product exposure during pregnancy, deaths of patients, cases involving the new risk identification or new aspects of known risk characterisation. Actions for the subsequent collection of reported adverse reaction data and the resulting data should be documented.

415. Where the report of an adverse reaction contains no information on the patient's age, steps should be taken to obtain this information or data on the age group due to the particular importance of this information for assessing safety in special age groups, including pediatric and elderly patients.

416. The methods used for the subsequent collection of adverse reaction data should optimize missing information collection. If possible, written confirmation of the data provided orally should be obtained. This standard pharmacovigilance activity should be carried out using measures that encourage the primary source (reporter) to submit new information that is important for the scientific assessment of the reported safety concerns. Using targeted questionnaires to collect additional important information about an adverse reaction allows the primary source to avoid the need to duplicate previously submitted data, makes it easier to complete, and helps optimize the important data collected for the evaluation. Targeted questionnaires should be developed in a form that facilitates completion as much as possible (e. g., using pre-filled fields) and the questionnaires should be translated into the Member States' languages.

417. If information about the suspected adverse reaction obtained directly from the patient or consumer is incomplete, attempts should be made to obtain consent to provide additional information from the healthcare

professional who may be provided with additional information on the adverse reaction. If a healthcare professional has confirmed (in whole or in part) the reported adverse reaction, this information should be accurately reflected in the individual adverse reaction report. In the event of subsequent full or partial confirmation of an adverse reaction by a medical professional, a note is made in the individual report of adverse reaction about the medical confirmation of this case.

418. With regard to suspected adverse reactions associated with the use of a biological medicinal product, accurate information about the manufacturer of the relevant medicinal product is of particular importance. Therefore, all appropriate measures should be taken to accurately indicate the trade name and the batch number of the biological medicinal product. Where it is impossible to accurately identify a batch of a suspected biological medicinal product, the description of the adverse reaction case in the initial individual report should include an appropriate indication of the request. The response to the reporter’s request for identification data for the batch of a suspected biological medicinal product is mandatory.

419. In particular cases, where it is impossible to collect information about an adverse reaction due to the anonymity of the reporter under the Member State’s legislation on personal data protection (e. g., in case of submitting a report about a medical error causing damage to the life or health of a patient and the reporter’s unwillingness to disclose personal data) the report shall be considered valid for submitting if the reporter’s organisation is capable of confirming the report directly with the reporter and the other minimum information criteria for the submitting are met.

4. Document Management

420. Reports of suspected adverse reactions should be stored on paper, in electronic form and handled in the same way as other medical records (including compliance with confidentiality requirements for patients and reporters' identifiability) in accordance with the Member States' legislation on personal data protection. Identifiable personal information about the reporting healthcare professional (reporter) should be kept confidential and protected from unauthorised access. The exchange of data between MA holders and authorised authorities regarding patients' and reporters' personal data should be organised, considering the requirements of the Member States' legislation on personal data protection.

421. To ensure the safety and confidentiality of pharmacovigilance data, strict control of access to documents and databases should be ensured, and they should be available only for the authorised pharmacovigilance personnel. The above data security requirement applies to all stages of the data flow and circulation. In this regard, procedures should be implemented to ensure data security and integrity during data transfer.

422. Where pharmacovigilance data transfers occur within an organisation or between organisations, a mechanism should be used in which there is evidence that all notifications have been received. In this case, a process of confirmation and/or reconciliation of information should be provided.

423. Authorised pharmacovigilance officers shall have access to electronically stored data in real-time mode.

424. The data entry procedure with the use of specific terminology shall be monitored and validated by performing a quality assurance audit systematically or by periodic sampling. Personnel shall be instructed in data

entry procedure using specific terminology, qualification of personnel must be periodically confirmed. Adverse reaction reports from the primary source (reporter) should be handled in an unbiased manner, without any change in information; adding or deleting information should be avoided during data entry or electronic data transfer. Reports shall include the verbatim text used in the primary source or an accurate translation. The original text shall be stated using appropriate terminology. To ensure the integrity of the information when encoding the report's text, terminology in the Member State's language or an accurate translation into English should be uses.

425. When storing electronic data, traceability ("audit trail") shall be ensured of all entered or changed data, including the information on dates and sources received and the dates and places to which these data are transmitted.

426. When entering data and generating summary reports, it is necessary to check the database to detect and process duplicate reports of adverse reactions.

5. Quality Management

427. The authorised authorities and MA holders should develop and implement the quality management system to ensure that the pharmacovigilance system meets the required quality standards at every stage in the handling of adverse reaction reports (e. g., at stages of data collection, data transmission, data management, data coding and archiving, case validation, case assessment, receiving follow-up information, when reporting of individual case safety and archiving a case).

428. The correctness of the information entered, including the consistency of the terminology used, is subject to quality control carried out systematically or using the principle of regular evaluation and random

sampling. The consistency of the stored data with the original reports and reports containing information on subsequent evaluation should be checked using quality control procedures that can validate the stored data by comparison with the original data or their images. In this regard, you should have constant access to the primary source data (e. g., letters, reports received (transmitted) by e-mail, records of telephone conversations containing detailed information about an adverse reaction), or images of the source data as graphic files.

429. Written standard operating procedures shall ensure that roles and responsibilities are clearly defined, and tasks are clear to all parties involved in handling the information on adverse reaction. Provisions shall be developed and implemented to ensure proper quality control and, if necessary, change the pharmacovigilance quality system. This requirement applies to activities contracted with third parties whose written standard operating procedures should be reviewed to ensure that such procedures are appropriate and meet applicable requirements of the Rules.

430. Appropriate training should be provided to personnel who directly carry out pharmacovigilance activities, as well as personnel who receive or process safety reports (for example, personnel from clinical development, sales, medical information, legal work, quality control) in terms of training in procedures for collecting and transmitting information on adverse reactions (events) to the pharmacovigilance department in accordance with the MA holder’s internal policy and the quality system procedures of the pharmacovigilance system. Training shall be conducted in the relevant sections of Union law, the legislation of the Member States in the field of pharmacovigilance and methodological documents in this area, and also include special training in safety report processing. Personnel charged with data entry shall be trained in the appropriate standards and terminology.

6. Special Situations

Using Medicinal Products while Pregnant or Breastfeeding

Pregnancy

431. Follow-up of cases where the embryo or fetus may have been exposed to medicinal product (through exposure to the mother or transfer of medication via sperm after exposure to the father) should be ensured to gather information about the outcome of the pregnancy and the possible effects of the product on child development. If the active ingredient (or one of the metabolites) has a long half-life, this should be considered when assessing the possibility of the medicinal product's exposure to the embryo or fetus through the mother or father if the product was taken before conception.

432. Ensure that reports of maternal and fetal drug exposure during pregnancy are as detailed as possible so that a causal link can be assessed. Standard questionnaires may be developed and used to assess such reports.

433. Individual cases with an adverse outcome associated with drug exposure during pregnancy are classified as serious adverse reactions that are subject to urgent reporting in accordance with the requirements of these Rules. Such reporting is applied to reports of:

a) congenital anomalies or developmental delays in the fetus or child;

b) fetal death and spontaneous abortion;

c) suspected neonatal adverse reactions that are classified as serious.

434. Reports of pregnancy termination cases without information on the presence or absence of a congenital disability, reports of a drug effect on pregnancy without information on the outcome, or reports with information on a normal outcome are not subject to urgent reporting because they do not clearly indicate the presence of a suspected adverse reaction. However, these

reports should be handled in the same way as other adverse reaction reports, with an assessment provided in a periodic safety update report.

435. In certain cases, all reports of maternal and fetal exposure to the drug during pregnancy may be subject to urgent reporting. This requirement may be a condition for marketing authorisation of a medicinal product or may be included in a risk management plan and, as a rule, due to the presence of a contraindication for the use of the medicinal product during pregnancy or its pronounced teratogenicity and the need for mandatory careful follow-up safety monitoring (e. g., for thalidomide, isotretinoin).

436. The Member States' authorised authorities should be immediately notified of the detection of a signal of a possible teratogenic effect (e. g., the signal of a group of similar abnormal pregnancy outcomes).

Breastfeeding

437. Suspected adverse reactions in infants after exposure to the medicinal product with the breast milk should be reported.

Use of the Medicinal Product in Pediatrics and the Elderly

438. Every effort should be made to establish and indicate the patient's age or age group (if an undesirable action is reported by a healthcare professional, patient or a non-patient consumer) to be able to identify potential safety signals specific to a particular age group.

439. Where a medicinal product use is common among patient populations not included in the approved general product profile, the authorised authorities and MA holders must monitor any subsequent safety concerns and take appropriate action to deal with alarms of these problems. MA holders and regulatory authorities should encourage healthcare

professionals to compile and report all suspected adverse reactions, even if these reactions occur in populations not included in the medicinal product's approved scope according to the summary of product characteristics.

Reports of a Medicinal Product Overdose, Abuse, Misuse, Medication Errors, and Occupational Exposure to Medicinal Products

440. If an overdose, abuse, misuse, medical error, or occupational exposure to a medicinal product did not lead to the development of an adverse reaction, information about them is not subject to the urgent reporting. This data should be recorded in an appropriate periodic safety update report and risk management plan (if applicable). Where these reports contain safety data affecting the risk–benefit ratio of a medicinal product, they should be notified to the Member States' authorised authorities in accordance with the requirements of these Rules. Subsequent collection of additional information is required to ensure that complete data is obtained regarding symptoms, names of suspected medicinal products, outcomes, type of non-compliance (e. g., errors of prescription, dispensing, dosing, unapproved indications, etc.).

Lack of Therapeutic Efficacy

441. Reports of lack of therapeutic efficacy should be recorded and follow up to obtain complete information. These reports are generally not subject to urgent reporting and are included in the data assessment in the periodic safety update report. In certain cases, it may be necessary to report the lack of therapeutic efficacy within 15 calendar days. Such cases include lack of therapeutic efficacy when a suspected medicinal product is used to treat life-threatening diseases (including life-threatening infectious diseases caused by susceptible microorganisms or accompanied by the emergence of a

new resistant strain of a microorganism previously considered susceptible), and when the suspected products are vaccines and contraceptives. An exception to this requirement would be if the reporter made a separate indication that the patient's outcome was due to disease progression and was not due to insufficient therapeutic efficacy of the medicinal product. Cases of therapeutic ineffectiveness identified in non-interventional post-authorisation efficacy studies, as components of the primary endpoints of this type of study, are also not eligible for reporting.

442. In the case of detection of therapeutic inefficacy issues during antibiotic therapy, it is not required to report cases caused by the use of antibiotics without considering the spectrum of action and sensitivity of the pathogen. Cases of therapeutic ineffectiveness during antibiotic therapy of life-threatening conditions caused by the emergence of new resistant strains of a previously considered sensitive microorganism are subject to immediate reporting.

443. Cases of vaccine inefficacy should be reported to highlight potential signals of reduced immunogenicity in the vaccinated subset, reduced immunity, or strain substitution. Such signals may require prompt action and further investigation in post-authorisation safety studies.

7. Urgent Submission of Individual Case Safety Reports

444. Only valid adverse reaction reports are subject to submission to the authorised authorities. The countdown for the urgent reporting procedure begins from the moment when the minimum required information for submitting a report in accordance with paragraph 407 of these Rules has become available to the MA holder (including medical representatives and contractors). This date is a starting date ("day zero"). It is considered the first day of receipt by the authorised authority or the MA holder of information on

a valid individual report about an adverse reaction, including weekends or holidays.

445. If the MA holder outsources a part of the pharmacovigilance activity, it is necessary to ensure that there are clear procedures in the form of a written document or detailed agreements on the division of pharmacovigilance obligations between the outsourcing organisation (person) and the MA holder to fulfill the obligations to submit valid reports of adverse reactions within the required time frame. These procedures shall determine, in particular, the processes for the exchange of safety information of the medicinal product, including the time intervals for the submission of information and the obligation to submit adverse reaction reports to the authorised authorities of the Member States. Duplicate transmission of reports to the authorised authorities of the Member States should be avoided.

446. For individual case safety reports described in the scientific and medical literature, the countdown (“day zero”) starts from the date of notification of publication containing the minimum information required under paragraph 407 of these Rules. If the outsourcing person or organisation is contracted to perform literature searches and/or report adverse reactions, detailed written assignment agreements are required to ensure that the MA holder can comply with the requirements of these Rules for reporting.

447. If additional important information is received about an adverse reaction report, the timing for a subsequent adverse reaction report is restarted (i. e., the date for a subsequent report is counted from the date of receipt of important additional information). Important additional information is considered new medical or administrative information about a suspected adverse reaction that may affect the assessment or management of a case or change its seriousness assessment. Non-material supplementary information

includes updated comments on case assessment performed or correction of grammatical or punctuation errors in a previous case report.

8. Requirements for Urgent Submission of Adverse Reaction Reports

448. Within 15 calendar days from receiving the minimum required information by the MA holder or his/her authorised representative in accordance with paragraph 407 of these Rules, MA holders submit to the Member State’s authorised authority:

Report of a serious adverse reaction detected in the territory of a Member State.

Report of an unexpected serious adverse reaction detected in the territories of other states.

The established reporting period applies to primary and additional information about an adverse reaction.

9. Cancellation of an Individual Adverse Reaction Report

449. The procedure for cancellation of an individual case safety report shall be used to indicate the invalidity of a previously submitted report (e. g. where the whole case is found to be in error). The procedure for canceling individual case safety reports is determined in paragraphs 535–537 of these Rules.

10. Making changes to an Individual Case Safety Report

450. Where it is necessary, (e. g., following internal or expert assessment) to make changes to a previously submitted individual case safety report (e. g., in terms of terminology, seriousness criteria, assessment of causal link, provision of a translation or article from a scientific medical

literature) that do not meet the requirements for submitting a report of important additional information as specified in paragraph 447 of these Rules, such changes may be made as determined in paragraphs 533 and 534 of these Rules.

11. Way and Format for Reporting Adverse Reactions

451. MA holders submit electronic adverse reaction reports to the Member State's authorised authority. The format of adverse reaction reports should comply with the format determined by the International Conference's guidelines on Harmonisation of Technical Requirements for Medicinal Products for Human Use "Clinical Safety Data Management. Data elements for reporting individual adverse reactions" (hereinafter referred to as the E2B electronic data format) (with account for transition from the version R2 of E2B electronic data format to the version R3 of E2B electronic data format). Individual reports are composed using MedDRA terminology and it is mandatary to use lowest level terms (LLT) in such reports. MA holders shall ensure compliance with the recommendations of MedDRA supporting service organisation in order to timely transfer to new versions of the MedDRA terminology.

452. The procedure for submitting individual adverse reaction reports in electronic format is determined by the relevant leadership of the Member States' authorised authorities.

12. Collection of Adverse Reaction Reports

Obligations of the Member States' Authorised Authorities

453. Authorised authorities of each Member State shall have a system for collecting and managing all reports of suspected adverse reactions

associated with the use of medicinal products in circulation in the Member States territories.

454. The authorised authorities of each Member State may encourage healthcare professionals in their Member State to report suspected adverse reactions. In addition, the Member State's authorised authorities may impose special obligations on healthcare professionals to report suspected adverse reactions.

455. To optimize the procedure for submitting information on adverse reactions, standard forms suitable for direct filling shall be freely available on the websites of authorised authorities (authorised organisations) in the Internet along with information on various ways of presenting data on suspected adverse reactions. The Member States' authorised authorities shall ensure that all reports of serious adverse reactions detected in the Member States territories, submitted to the Member State's relevant authorised authority and assessed as valid, shall be included in the Member State's unified adverse reactions database.

456. The Member States' authorised authorities should ensure that "gratitude" for reporting adverse reactions is expressed, including providing the reporters with information on the results of further consideration of their adverse reaction reports.

457. When receiving adverse reaction reports from MA holders, the authorised authorities of the Member States, in whose territories the suspected adverse reaction occurred, have the right to involve patients and MA holders in follow-up on these reports. MA holders may be involved in the follow-up on the received adverse reaction reports in the following cases:

a) necessity to obtain some important additional information to perform a proper assessment of an adverse reaction;

b) necessity to clarify the conflicting data provided in the adverse reaction report;

c) necessity to obtain additional information as part of a signal validation procedure, assess aspects of a safety profile, evaluate a periodic safety update report, or confirm safety concerns in the risk management plan.

458. Each Member State shall ensure the following:

providing information to the authorised authority responsible for medicinal product circulation control on any suspected adverse reaction which has become known to any authorised authority, department, organisation, or institution responsible for patient safety;

reporting any suspected adverse reaction to that Member State’s database.

Where the reports of suspected adverse reactions were sent to other government bodies, departments, organisations, or institutions in this Member State, the Member State’s authorised authority, whose competence includes exercising pharmacovigilance, shall have data exchange agreements with them for these reports to be sent to this Member State’s authorised authority. Information about adverse reactions in these cases shall be transmitted to the Member State’s authorised authority in electronic form. This requirement also applies to cases of adverse reaction developed due to medical errors.

459. Data and documents on pharmacovigilance concerning authorised medicinal products are subject to storage in the authorised authority for at least 10 years after the marketing authorisation expiration. The legislation of the Member States may specify a longer storage period.

460. Member States do not establish additional obligations for MA holders to submit adverse reaction reports, in addition to those established by

these Rules, if this does not have sufficient grounds obtained from the results of pharmacovigilance activities.

Obligations of MA Holders

461. Each MA holder shall establish and maintain a system for collecting and recording all reports of suspected adverse reactions that come to his or her attention, whether through spontaneous reporting by healthcare professionals, patients, or consumers or during post-authorisation studies. Procedures shall be developed and implemented by MA holders to provide accurate and verifiable data for the subsequent scientific evaluation of adverse reaction reports. The MA Holder is not entitled to reject or fail to comply with the required procedures for handling the adverse reaction reports should this information be received. MA holders shall establish mechanisms to ensure that reports can be tracked, adverse reaction reports can be followed up, and updates on adverse reactions can be submitted to the authorised authority.

462. Pharmacovigilance data and documents for authorised medicinal products are subject to storage by the MA holder for at least 10 years after the marketing authorisation expiration. The legislation of the Member States may specify a longer storage period.

463. The obligation to collect information about suspected adverse reactions by MA holders extends, among other things, to reports of medicinal products whose ownership by this MA holder cannot be excluded based on one of the following criteria specified in the report of a suspected adverse reaction: trade name of the medicinal product, name of the active ingredient, dosage form, series or route of administration. Exclusion of the medicinal product ownership by this MA holder based on information from the Member State, the primary source, or the Member State where the suspected adverse

reaction occurred can be applied, provided the MA holder can confirm that the suspected medicinal product has never been placed on this Member State's market and is not a product that can be brought to this Member State territory as a travel aid (e. g., medicines for malaria treatment).

464. The MA holder shall ensure that all companies owned by him/her are informed of all adverse reaction reports received by him/her as regards the medicinal product for which he/she holds the marketing authorisation. This requirement shall also be met if a commercial agreement is concluded for one of the MA holder's medicinal products. Information is provided by the MA holder's entering of information on incoming adverse reactions into the database and further database functioning as a single point of access to safety data.

Spontaneous Reports

465. MA holders shall record all spontaneous reports of suspected adverse reactions occurring in the territory of Member States or beyond. The requirement applies to reports of suspected adverse reactions received electronically or by any other means. MA holders may use their websites on the Internet to facilitate the collection of suspected adverse reactions by placing adverse reaction forms or appropriate contact details for direct communication.

Solicited Reports of Suspected Adverse Reactions

466. MA holders shall record all reports of suspected adverse reactions occurring in the Member States' territories or beyond and identified during post-authorisation studies. These solicited reports include reports from an organised data collection initiated, managed, or funded by MA holders. These

reports also include information received during non-interventional post-authorisation studies, compassionate use programs, personalised off-label drug use programs, other patient support, disease monitoring programs, patient support programs, gathering efficacy or adherence information, and registry maintenance. Concerning non-interventional post-authorisation studies, this requirement applies to studies based on primary data collection; the data collection procedure is given in paragraphs 468–473 of these Rules.

Reports Received During Non-Interventional Study

467. MA holders must implement and use mechanisms to collect complete and comprehensive information on cases of suspected adverse reaction in the initial reporting of a suspected adverse reaction as a result of spontaneous reports of such reactions to allow proper evaluation of the report and fulfill the requirements for urgent reporting to the Member States' authorised authority (where applicable) of the investigational (or supplied) medicinal product. MA holders shall establish a system that provides report traceability, the possibility of follow-up on adverse reaction reports and obtain the primary source evaluation results regarding the relationship between the investigational (supplied) medicinal product and the adverse event. In the absence of information regarding the primary source's opinion on the existence of a relationship, the MA holder, based on the available information, shall carry out his/her own assessment of the relationship, determining the validity of the report and compliance with the reporting criteria. This requirement does not apply to studies designed to reuse medical data. Adverse reactions identified in a study with the secondary use of data are not subject to submission to the authorised authority. Adverse reaction data from organised data collection shall be reflected in a periodic safety update report.

468. If suspected adverse reaction data are derived from non-interventional studies, data from studies with primary data collected directly from patients and healthcare professionals, and data received from studies with designs that rely on secondary use of data (e. g., studies based on medical record or electronic healthcare record reviews, systematic revisions or meta-analyses).

469. The report is drawn up if the reporter or the MA holder suspects that there is at least a possible causal link with the suspected medicinal product. Adverse event reports in which causality is assessed as doubtful should be included in the final study report.

470. For non-interventional studies with initial data collection directly from patients and healthcare professionals, adverse reaction reports for which the reporter or MA holder suspects at least a possible causal link with the suspected medicinal product shall be submitted. Investigators should direct other reports to the Member State’s authorised authorities if the reports describe suspected adverse reactions not related to investigational medicinal products and no interaction with the investigational products has been established for them (where applicable).

471. In the conduct of non-interventional studies based on secondary use of data, reporting of detected adverse reactions is not required. All data on identified adverse reactions are summarised in the final research report

472. The MA holder has the right to clarify the requirements for the submission of individual adverse reaction reports to the Member State’s relevant authorised authorities.

473. The MA holder should comply with the legislation of the Member State applicable to reporting cases of suspected adverse reactions to Member State’s independent ethics committees and investigators.

Compassionate Use Program, a Personalised Unauthorised Medicinal Product Use Program

474. If a MA holder or healthcare professional is notified of a suspected adverse reaction or detects a suspected adverse reaction as part of a compassionate use program or a personalised unauthorised medicinal product use program, adverse reaction reports are submitted as follows:

a) where an adverse reaction has been detected in the course of organised data collection, only adverse reactions with a causal link to the suspected product should be reported as possible (at a minimum) by the primary source (reporter) of the report or by the MA holder. These reports should be considered as solicited adverse reaction reports.

b) where an adverse reaction was not detected through an organised data collection, all adverse and unintended reactions to the medicinal product should be considered unsolicited reports of suspected adverse reactions and presented as a corresponding report.

Patient Support Program

475. Patient support programs are a type of organised data collection system where a MA holder collects data related to medicinal product use in patient populations. Examples of post-authorisation patient support programs are disease monitoring programs, patient monitoring, patient adherence data collection, and monitoring as part of compensation (reimbursement) systems.

476. It is permissible to actively collect information on adverse reactions during the execution of various types of organised data collection systems. These adverse reaction reports should be counted as solicited reports. The MA holder shall ensure that there is a mechanism for the organised and systematic collection of safety data following the implemented program and ensuring the submission of adverse reaction reports to the

authorised authority in accordance with the requirements of paragraph 448 of these Rules in case the information on adverse reaction complies with the criteria for urgent reporting.

477. If an adverse reaction has been identified in an organised data collection system outside the organised and classified safety data collection process, all adverse and unexpected drug reactions that have been reported to the MA holder by the healthcare provider or the patient should be treated as unsolicited reports of suspected adverse reactions and submitted accordingly.

Reports Published in the Medical and Scientific Literature

478. MA holders should monitor publications in the scientific and medical literature in all states where the use of the relevant medicinal products is permitted in accordance with paragraphs 393–397 of these Rules and submit detected reports of adverse reactions to the authorised authorities of the Member States in accordance with the requirements of these Rules.

479. Adverse reaction reports detected when monitoring publications of scientific medical literature, are not subject to urgent reporting in the following cases:

a) where the MA holder’s ownership of a medicinal product can be excluded based on the product’s trade name specified in the report, the name of the active ingredient, dosage form, the route of administration, and the batch number;

b) where the MA holder’s ownership of the medicinal product can be excluded based on the country of origin of the report or the country of the primary source of the suspected adverse reaction specified in the report if the MA holder did not supply the product to this territory;

c) where the publication is the result of analysis by the authorised authority of the adverse reactions database; (the exception does not apply to

publications generated based on the analysis of databases of other authorised authorities);

d) where the publication contains information from public databases that present cases in tables or line-by-line lists. The exclusion does not apply to publications that allow you to generate a valid individual case safety report.

e) where the publication presents the results of post-authorisation studies, meta-analyses, or scientific reviews;

f) where the publication provides information on adverse reactions in a patient group in conjunction with the use of a certain medicinal product, and there are no individual patient data that allow the formation of a valid individual case safety report.

480. The safety information presented in such scientific publications should be considered in the relevant sections of the periodic safety update report and taken into account when analyzing the effect of this information on the medicinal product’s risk–benefit ratio. Any new safety information that may affect the medicinal product’s risk–benefit ratio should be immediately notified to the Member State’s authorised authority where the product is authorised.

Suspected Adverse Reactions Arising from a Quality Defect or Counterfeit Medicinal Products

481. If the report of a suspected adverse reaction is related to the medicinal product used, the falsification of which is suspected or established, or a product of inadequate quality, this report must be submitted (if classified as a valid report).

482. In these cases, public health protection may require urgent action, such as recall from the market one or more defective batch of the medicinal

product. MA holders should use a system that ensures an immediate assessment and investigation of the received report of a suspected adverse reaction arising from a counterfeit medicinal product or a defect in a product's quality. In case of confirmation of the presence of a quality defect, the MA holder's immediate notification to the direct manufacturer of the medicinal product and the Member States' authorised authorities is required.

Suspected Transmission of an Infectious Agent through Medicinal Product

483. An infectious agent is any microorganism, virus, or infectious particle (e. g., transmissible spongiform encephalopathy-associated prion protein), pathogenic or non-pathogenic.

484. Suspected infectious agent transmission due to a medicinal product use is considered a serious adverse reaction, subject to urgent reporting within 15 calendar days from the date of receipt by the MA holder or his/her authorised representative of the minimum required information on adverse reaction in accordance with paragraph 407 of these Rules. This requirement also applies to vaccines.

485. MA holders of medicinal products obtained from human blood or plasma shall have a system that provides, in case of suspicion of an infectious agent transmission, immediate notification of the product's manufacturer, relevant authorised authorities for controlling the circulation of blood products, and authorised authorities of the Member States.

486. Transmission of an infectious agent can be suspected based on clinical signs or symptoms and laboratory test results that indicate an infection in a patient exposed to a medicinal product. Particular attention should be paid to detecting infections or infectious agents known to be

transmissible due to a medicinal product. Still, the risk of unknown pathogens should also be considered.

487. Assessment of suspected transmission of an infectious agent due to a medicinal product use should be carried out with extreme caution and ensure, as far as possible, a distinction between routes of infection (e. g., injection or another route of administration), source of infection (e. g., drug contamination), and the patient’s clinical condition at the time of suspected infection (immunosuppressive condition or prior vaccination).

488. Confirmation of contamination (including inappropriate inactivation or weakening of virulence (attenuation) of infectious agents as active ingredients) of a suspected medicinal product increases the degree of evidence of transmission of the infectious agent and the suspicion of a defect in the quality of the medicinal product.

13. Emerging Safety Issues

489. When using medicinal products, events or observation results may be detected that can have a significant impact on the risk–benefit ratio of the medicinal product, patient, or public health (health of population), which requires an immediate assessment by the authorised authority and may require urgent regulatory measures, and informing healthcare professionals and patients. Submission of information on identified emerging safety issues is carried out in accordance with the requirements established in paragraphs 756 and 757 of these Rules. If individual cases of suspected adverse reactions were the basis for identifying an emerging safety issue, the requirements for the submission of adverse reaction reports shall be met.

14. Reporting of Adverse Reactions in the Period Between Applying for Marketing Authorisation of a Medicinal Product and Obtaining a Certificate of Marketing Authorisation

490. In the period between applying for marketing authorisation of a medicinal product and obtaining a certificate of marketing authorisation, the prospective MA holder may receive information (on quality, clinical or preclinical data) that changes the medicinal product's risk–benefit ratio. The MA holder's responsibility is to ensure the immediate submission of this information to the Member State's authorised authority that conducts the expert assessment and authorisation of the medicinal product, in accordance with the requirements of paragraphs 756 and 757 of these Rules.

491. Where the MA holder receives information about adverse reactions detected during the medicinal product use in other countries, the valid individual adverse reaction reports generated based on the solicited and unsolicited reports shall be submitted to the authorised authority in accordance with paragraph 484 of these Rules.

15. Reporting of Adverse Reactions in the Period after Suspension or Withdrawal of a Marketing Authorisation Certificate

492. The MA holder shall continue to collect information on suspected adverse reactions associated with the medicinal product in question after the suspension of the marketing authorisation with the implementation of reporting in cases that meet the criteria for urgent reporting in accordance with paragraphs 431–448 of these Rules.

493. If the marketing authorisation is withdrawn, authorised authorities shall request that the MA holder continue collecting information on suspected adverse reactions to the medicinal product (e. g., to facilitate the assessment

in the event of delayed adverse reactions or to receive retrospective adverse reaction reports).

16. Reporting of Adverse Reactions During Public Health Emergencies of International Concern

494. In the event of a public health emergency of international concern established by the World Health Organisation, the authorised authorities are entitled to make changes to the requirements for the frequency of reporting suspected adverse reactions. Such changes are adopted separately for each emergency, and notifications about them are posted on the official websites of the Member States' authorised authorities in the Internet.

17. Submitting Reports Based on Lawsuits for Harm Caused by the Use of Medicinal Products

495. Reports arising from lawsuits on medicinal product use should be handled as unsolicited reports. Only valid adverse reaction reports should be submitted where the reporter or MA holder suspects that there is at least a possible causal link between the adverse effect and the suspected medicinal product. In these cases, when determining compliance with the criteria for urgent reporting, valid individual case safety reports shall be submitted to the Member States' authorised authority in accordance with paragraphs 431–448 of these Rules.

496. When receiving a large number of potential reports of serious adverse reactions, the MA holder, as an exception, may agree with the authorised authority to extend the deadline for submission of individual reports to 30 calendar days.

18. Reporting Cases of Use of a Medicinal Product Not Following the Summary of Product Characteristics or the Package Insert

497. The use of a medicinal product not following the summary of product characteristics or the package insert may be due to various reasons. Examples include cases of the use of a medicinal product with deliberate non-compliance with the conditions defined in the approved current information on the medicinal product (summary of product characteristics or package insert), such as:

a) the use of a medicinal product not following the approved indications.

b) the use in a patient group where the product is not recommended to use;

c) the difference in route of administration;

d) the difference in the dosage regimen.

498. The need to submit reports on cases of a medicinal product use that does not comply with the summary of product characteristics for medical use or package insert is determined based on the following conditions according to the result of use regarding harm to the patient’s health or life:

a) the use of a medicinal product not following the summary of product characteristics or the package insert causing harm to the patient due to the development of a suspected adverse reaction;

b) the use of medicinal product not following the summary of product characteristics or the package insert without causing harm to the patient and a suspected adverse reaction.

499. In case of receiving information about the development of an adverse reaction, a MA holder takes measures to subsequently collect information on the adverse reaction to provide as complete data as possible for each of the reports. The submission of valid individual case safety reports

resulting from the medicinal product not following the summary of product characteristics or the package inserts is carried out in accordance with paragraphs 431–448 of these Rules in case of determination of compliance with the criteria for urgent reporting.

500. Where applicable, the assessment of the risk–benefit ratio of the medicinal product in the periodic safety update report shall include the clinically significant risks of using the medicinal product, not following the approved information for the medicinal product use.

501. In accordance with Section VI of these Rules, if there is evidence-based evidence of the relationship between the development of clinical adverse outcomes and the use of a medicinal product not following the summary of product characteristics or package insert, an adverse reaction can be assessed as a potential risk, or, in the case of meeting the criteria for an important safety concern as an important potential risk with the inclusion in the safety specification of a risk management plan. This approach is especially essential in cases where the detected aspect of the safety profile is characterised by significant differences between the general population and the population in which the medicinal product was not used following the approved information on the medicinal product use. The inclusion of a safety concern in the list of important potential risks of the risk management plan requires the implementation by the marketing authorisation of measures to assess this important risk as part of the pharmacovigilance plan.

502. The MA holder shall ensure the collection and assessment of information on the use of the medicinal product, not following the summary of product characteristics or the package insert, to fulfill the obligation to continuously evaluate and inform the authorised authority about all changes in the risk–benefit ratio of the medicinal product.

503. The risk management plan includes assessing aspects of the use of the medicinal product in the context of routine clinical practice and determines an approach proportional to the identified risks for further monitoring and study. If the use of a medicinal product is determined not following the summary of product characteristics or the package insert as a safety concern, that is, where a relationship is established between this non-compliance with the approved conditions for the use of the medicinal product and an important potential risk, in terms of risk management, and assessment of the need to perform the following pharmacovigilance activities:

Development of targeted questionnaires for the subsequent collection of information on adverse reactions resulting from the use of a medicinal product not following the summary of product characteristics or package insert.

the use of other mandatory forms of routine pharmacovigilance activities in the form of targeted collection of individual reports of drug use cases not following the summary of product characteristics or package insert, not accompanied by the development of adverse reactions;

conducting special studies (such as application studies, database evaluations).

504. Individual reports of using a medicinal product not following the summary of product characteristics or package inserts, which were not accompanied by the development of adverse reactions, are not subject to submission to the authorised authority since they do not meet the minimum criteria for compliance with valid reports.

505. Medicinal products that do not have a developed and approved risk management plan shall also be assessed by the MA holder and authorised authority for possible safety concerns due to their application not following the summary of product characteristics or package insert. If this safety

concern is identified, the need to develop a risk management plan or conduct a post-authorisation safety study is determined.

19. Preparation of Individual Case Safety Reports

General Principles of Preparing Individual Reports of Adverse Reactions

506. All parties exchange individual adverse reaction information electronically, using MedDRA terminology and following the applicable E2B electronic data format. The information in the submitted individual report shall be as complete as possible to carry out the adverse reaction assessment. If it is clear that the reporter has not sent the full available information on an individual case, the recipient may request a resubmission of the individual case safety report, including full information following the electronic filing requirements within 24 hours for subsequent medical evaluation and use in the signal detection procedure.

507. Suppose a suspected adverse reaction, information about which is presented in the form of an individual report, can significantly impact the risk–benefit ratio of a medicinal product. In that case, this information is assessed as an emerging safety issue that must be submitted to the authorised authority as an individual report and as an emerging safety issue in accordance with paragraphs 756 and 757 of these Rules. In this case, the reasons for classifying the information in this report as an emerging safety issue and the proposed measures are included in the “Reporter Comments” section according to the E2B electronic data format of the individual adverse reaction report.

Examples of emerging safety issues include but are not limited to:

serious safety issues identified in ongoing or completed studies (e. g., unexpected increases in fatal or life-threatening adverse events);

serious safety concerns detected based on spontaneous reports or data published in the scientifical medical literature, which may be the basis for the addition of contraindications, restrictions on the use of the medicinal product, or the need to withdraw it from the market;

regulatory actions concerning serious safety concerns in third countries (e. g., restricting the use of a medicinal product or temporary suspension of a certificate of marketing authorisation).

Information about Suspected, Interacting, and Concomitant Medicinal Products

508. An adverse reaction report should include the names of the suspected, interacting, and/or concomitant medications, their dosage regimens, and the start and end dates of therapy. The classification of medicinal products as suspected, interacting, or concomitant is based on the primary reporter's assessment of the adverse reaction. In case of disagreement between the authorised authority or the MA holder with the characterisation of the role of medicinal products made by the primary source of the adverse reaction report, this discrepancy is reflected in the "Reporter Comments" section according to the E2B electronic data format of the individual adverse reaction report, while retaining the primary assessment of the reporter.

509. For combination medicinal products that contain more than one active ingredient, each active ingredient must be indicated separately. If there is information about the trade name of the suspected or interacting medicinal product, the trade name and name of the active ingredient(s) shall be indicated. If relevant information is available for a suspected or interacting medicinal product, the state in which the patient received the product, the

marketing authorisation number, the state in which the product was authorised, and/or the batch number are also indicated.

Suspected Relationship with the Therapeutic Class of a Medicinal Product

510. Where the suspected medicinal product does not have a trade or international name (e. g., only the therapeutic class is indicated as the primary source of an adverse reaction report) or where it is impossible to structure the prescribed therapy, the absence of this information is indicated in the case description section and is not included in the structured data elements of medicinal product names or active ingredients. A similar principle applies when describing drug interactions with food (e. g., with grapefruit juice). If an adverse reaction report is submitted as being related to a therapeutic class of medicinal products, the report is considered incomplete and does not meet the criteria for prompt submission to authorised authorities. In this case, the person responsible for submitting the report to the Member States' authorised authorities must take the necessary measures to collect the missing information about the suspected medicinal product.

Suspected Drug Interactions

511. When describing drug interactions, which may include the interaction between medical products (including biological products), as well as the interaction of medicinal products with food, medical devices and alcohol, coding of suspected interaction and entering information about the interaction-related adverse reaction is performed in accordance with the recommended MedDRA terminology and the following sections of the E2B eData format:

To describe the drug interaction, under “Characterisation of the Role of the Medicinal Product” for all interacting substances, the characteristic “interacting medicinal product” is selected;

b) to describe the interaction of a medicinal product with food or other non-medicinal agents, information on the interacting medicinal product is included under “Information on the medicinal product,” information on the interacting non-medicinal agent is included in the case description.

Suspicion of an Interaction with a Medicinal Product’S Excipient

512. Where the primary source of the adverse reaction report suspects the possible role of one of the excipients in the development of an adverse reaction (e. g., a dye, preservative, stabilizer, flavoring agent, etc.), information on the suspected excipient is provided separately in “Information on Medicinal Product” section, reflected in the description of the case and (if any) “Patient Study and Tests Results” section provides data of the test results (positive or negative), which suggest the presence of a relationship between an adverse reaction and one of the product’s excipients.

Important Additional Information on the Medicinal Product

513. Additional information on the medicinal product, which may be essential for performing data analysis and assessing the adverse reaction case, shall be included in the report in the “Additional Information on the Medicinal Product” section with the appropriate selection of subsection and coding of the additional characteristic according to the MedDRA terminology attribution:

counterfeit medicinal product;

overdose;

the medicinal product was taken by the patient’s father;

the medicinal product was taken after the expiration date;

series test results confirmed compliance with specifications;

series test results demonstrated deviation from specifications;

medication error;

misuse;

addiction;

occupational exposure;

use not following the summary of product characteristics or package insert.

Examples of use not following the summary of product characteristics or package insert include intentional use for a different indication, a different group of patients (e. g., a different age group), a different route or method of administration, or in a different dosage. To determine whether a medicinal product’s use meets the criteria for off-label use, the summary of product characteristics or package inserts are applied, approved in the country where this medicinal product is used.

514. The “Reporter Diagnosis” section may include a description of signs and symptoms that support a particular diagnosis and describe the role of the suspect product in “Reporter Comments” section. Where the reporter does not make specific instructions regarding additional product characterisation, but it is evident from the report’s clinical context, the reporter may at its discretion add additional product characterisation information to the specified section. In this case, follow-up steps should be taken to obtain additional information. The “Additional Information on the Medicinal Product” section intended for a free text can be used to indicate any additional information in this section (e. g., expiration date for the specified batch of the medicinal product).

Suspected Adverse Reaction

515. A report of a suspected adverse reaction shall include all available information about such reaction. The required data includes:

the onset and end dates of the adverse reaction (or duration);

the adverse reaction seriousness;

the outcome of the adverse reaction at the date of the last observation;

the time interval between the onset of the suspected medicinal product and the onset of the adverse reaction;

the description of the adverse reaction by the primary source of the report;

the state in which the adverse reaction has been detected.

516. The coding of diagnosis, provisional diagnosis, or symptoms and signs of adverse reaction is performed using the current version of the MedDRA dictionary and according to the lowest level terms. Where the report specifies the patient’s diagnosis, characterizing the development of an adverse reaction and the characteristic symptoms of the manifestation of this condition, it is preferable to encode the immediate diagnosis according to the MedDRA lowest level terms. In the absence of a diagnosis, all symptoms and abnormalities included in the report shall be reflected using the appropriate MedDRA term. If these symptoms are typical clinical manifestations of a certain diagnosis, it can be additionally entered in the adverse reaction section following the MedDRA terminological classification by an authorised authority or a MA holder as part of the diagnosis or the reporter’s comment.

517. Where the primary source of the adverse reaction report specifies in the adverse reaction description its symptoms that are not typical clinical manifestations of the original diagnosis and suspects that these symptoms are

adverse reactions, such symptoms shall be reported and classified as appropriate according to MedDRA terminology.

518. In case the authorised authority or the MA holder disagrees with the diagnosis reported by the primary source of the adverse reaction report, the alternative diagnosis may be included in the reporter's diagnosis section, stating the grounds for disagreement with the reporter regarding his/her comments.

519. In the event of a patient's death, the report shall include information on the date and cause of death, including (if any) autopsy data. If this information suggests that a patient's death is not related to an adverse reaction and is due to other causes (e. g., disease development, death should not be used as a criterion of the adverse reaction seriousness).

Adverse reaction description and Causal Link Assessment

520. For each individual report, description of the developed adverse reaction is provided if the necessary data is available in the primary source of the adverse reaction report. The description is mandatory for serious adverse reactions. Information about the development of an adverse reaction shall be presented in a logical and temporal sequence, following the chronology of changes in the patient's condition, including the clinical course, therapeutic measures, outcome, and subsequent information received.

521. The description shall be comprehensive and act as an independent medical report containing all known important clinical data and related information (laboratory, diagnostic and other information), including patient characteristics, treatment details, medical history, the clinical course of manifestations, diagnosis, adverse reactions, and their outcome, important laboratory data and any other information that confirms or refutes suspected adverse reactions. In case of the patient's death, the main results of the

autopsy or postmortem examination (if applicable) shall be summarised. Information on the case is included in “Case Summary” of the adverse reaction report in E2B format.

522. The primary source’s comments on the adverse reaction report in terms of diagnosis or causal link assessment are provided in “Reporter Comments” section in electronic data format.

523. The authorised authorities of and MA holders have the right to make comments or propose an alternative option regarding the diagnosis or assessment of the causal link between the suspected medicinal product and an adverse reaction in disagreement with the primary source of the report (reporter). Comments, in this case, are presented in “Reporter Comments” section.

524. An assessment of the credibility of the assumed causal link between each medicinal product and each reported adverse reaction is submitted in a structured manner. A report may include an assessment made by different sources (primary reporter, MA holder, the authorised authority) using different causal link assessment methods. Information on the assessment of a causal relationship is reflected in the E2B(R3) electronic data format in the “Medicinal Product – Adverse Reaction (Event)” section.

Test Results and instrumental examination

525. The adverse reaction description should include the results of tests and procedures performed to diagnose or confirm the reaction (adverse event) (including tests performed to investigate a cause unrelated to the product (e. g., serological tests for infectious hepatitis when hepatitis caused by the product is suspected)). Positive and negative test results and instrumental examinations should be reported.

526. Information on the results of analyses and instrumental studies shall be presented in the report in a structured form following the current version of MedDRA terminology in “Results of Tests and Procedures Obtained during Patient Examination” section in the E2B electronic data format of an individual adverse reaction report, indicating the types of studies received results, the interval of normal values for the test indicators (if applicable) and the reporter’s comment on the results obtained. Where it is impossible to present information in a structured form, the data can be presented in text form in the part of the “Results of Tests and Procedures” section intended for entering free text.

Additional Documents and Information

527. Key information from additional documents to support the adverse reaction data shall be included in the appropriate sections of individual case safety reports. In the “Additional Available Documents” section of the E2B electronic format of an individual adverse reaction report, an instruction is made regarding the attachment of additional documents or information to the report, with the inclusion of documents directly in the sent report in the “Attachments” subsection.

If the reporter sends additional documents or information, the subsection “Documents at the Reporter’s Disposal” contains a description of the type of these documents (e. g., data from medical records, conclusion on the results of autopsy). The submitted additional documents and information shall be processed, considering the personal data protection legislation in force in the Member State territory.

20. Follow-Up Information

528. Considering the submission of an individual case safety report at different stages to different recipients, the report's status concerning initial or subsequent submission is determined at the recipient level. For this purpose, data on the report receipt date, the unique identifier of the individual report and the number assigned by the reporter are used. Exact report receipt dates are mandatory for determining the report status.

To ensure proper control of the information update and status of the report, the unique identifier of an individual case safety report and the date when the report was first received shall be kept unchanged at the level of authorised authorities and MA holders, reflected in "International Unique Identifier" and "Date when the Report was First Received" sections of the E2B electronic data format respectively. The identifier assigned by the reporter is included in "Unique Identifier of the Reporter of an Adverse Reaction Report" section. Upon receipt of further information by the MA holder or the authorised authority, the exact date of receipt of the latest information on an adverse reaction report is updated each time, regardless of the significance of this information in the section "Date of receipt of the latest information on an adverse reaction report" of the E2B electronic data format of an individual adverse reaction report. New follow-up information in part of the summary shall be included in the report in "Case Summary, Clinical Description, Therapeutic Measures, Outcome, and Additional Case Information" section of the E2B electronic data format with the ability to identify the updated piece of data and, where applicable, shall be presented in a structured form.

Important Follow-Up Information

529. Should any new important medical data be received, the reporter of an adverse reaction shall immediately send follow-up adverse reaction information. This information implies, among other things, new suspected adverse reactions, changes in the causal link assessment, and any new information (data) about a change in the original (prior) information about the case, where it affects the medical interpretation of the adverse reaction. Assigning the new adverse reaction data to new important information is based on the medical assessment of compliance with the above criteria.

530. It should be taken into account as significant changes in the information on adverse reactions, any situations in which, for individual cases of adverse reactions, the criteria for severity according to the definition of a severe adverse reaction and/or the assessment of causal link (e. g., the follow-up information causes a change in the seriousness criteria assessment from a serious adverse reaction to a non-serious adverse reaction, or a change in the causal link assessment from that having any level of relationship likelihood to a questionable relationship), and report such cases in accordance with the requirements for urgent reporting of adverse reactions.

531. Submission of a new version of an individual case safety report may be required when administrative information is received for the case that may affect the case management procedure. For example, the receipt of data on report identification parameters when performing the duplicate report control procedure should be reflected in “Other Case Identifiers during Previous Data Transmission” section. If the reporter submits additional documents to support a change in a previously completed medical assessment, the new documents are included in “Additional Documents Available” section for individual case safety reports in E2B electronic format.

Follow-Up Information that Does not Meet the Criteria for Important Follow-Up Information

532. If the follow-up information makes minor changes to the original data and the adverse reaction is assessed, it is not subject to immediate submission. The changes made in individual chronological dates while describing and assessing an adverse reaction, which do not affect the assessment or the case transferring, and correction of typos in a previous case version or typographical errors in a previously submitted report, are considered minor changes. However, an expert medical opinion should be obtained regarding the relevance of the follow-up information since the formal assessment is insufficient (e. g., a change in the report of an adverse reaction to a patient's date of birth constitutes a significant change in the patient's age information if it results in the transfer of information about an unwanted medicinal product's action on patients of a different age group). A change in the MedDRA term used in connection with a version update of the dictionary may also be assessed as a non-significant change if the change does not affect the medical assessment of the adverse reaction case.

21. The Procedure for Making Changes to Individual Adverse Reaction Reports

533. General procedure for making changes to an individual report about an adverse reaction submitted to an authorised authority are determined by paragraph 450 of these Rules. Making changes is necessary when a correction is made to a previously submitted report based on the results of an internal or expert evaluation that is not based on new information that requires a subsequent adverse reaction report. If the change introduced affects the case's medical assessment, the individual report shall be resubmitted with the inclusion of information on the change in the case description. For

example, a change to the MedDRA terminology code due to a revision of a previously performed medical interpretation of an adverse reaction case may be considered a material change and requires the resubmission of an individual case safety report in the format of making changes (see paragraphs 529–532 of these Rules for examples of information that meets and does not meet the criteria of important one).

When making changes to an individual adverse reaction report in the sections “International Unique Identifier,” “Date when the Report was First Received from the Primary Source,” “Unique Identifier of the Adverse Reaction Reporter,” “Date of Receipt of the Latest Information on the Adverse Reaction Report,” “Reporter’s Organisation” remains unchanged, in the “Report Cancellation or Changing” section, the option of making changes to the previously submitted individual case safety report is selected, indicating the appropriate basis in “Basis for Cancellation or Changes” section.

534. Additional documents provided at the request of the authorised authority, such as translation of an individual report about an adverse reaction into Russian, supporting documents on the report or publication, which are referenced in the report, are submitted in the form of a change in the initial report with the inclusion of documents in “Attached Documents” section of E2B electronic data format of an individual case safety report.

22. Cancellation Procedure for an Individual Case Safety Report

535. The cancellation procedure for an individual case safety report shall be used to deny the validity of a previously submitted report, for example, if the entire case is found to be erroneous or if duplicate reports are found.

536. Cancellation of previously submitted individual case safety reports is subject to the following principles:

a) grounds for cancellation shall clearly and unequivocally state the reason why a previously submitted individual adverse reaction report is considered invalid. For example, grounds for cancellation stated like “the report no longer meets the criteria for reporting” or “the report was submitted in error” are insufficient justification for the cancellation procedure to be followed;

b) an individual adverse reaction report can only be canceled by the organisation that originally submitted this report;

c) in the event of cancellation, an individual adverse reaction report is not subject to subsequent restoration as valid;

d) separate follow-up reports to the original individual adverse reaction report are not subject to cancellation. Only a complete individual adverse reaction report to which follow-up reports have been generated may be revoked;

e) canceled individual adverse reaction reports are subsequently not included in the ongoing scientific assessment of the safety data as they are considered invalid. However, such reports should be saved in the reporter and recipient’s pharmacovigilance database for subsequent audit.

537. When performing the cancellation procedure for an individual case safety report, information in the sections “International Unique Identifier,” “Date when the Report was First Received from the Primary Source,” “Unique Identifier of the Adverse Reaction Reporter,” “Date of Receipt of the Latest Information on the Adverse Reaction Report,” “Reporter’s Organisation” shall remain unchanged, while in the “Report Cancellation or Changing” section, the option to cancel the previously submitted individual case safety report is selected with indication of the appropriate basis in “Basis

for Cancellation or Changes" section. Where a subsequent submission of a previously canceled individual adverse reaction report is required, new identification numbers are assigned to the report in the "International Unique Identifier" sections "Unique Identifier of the Adverse Reaction Reporter."

23. Legislation on Personal Data Protection

538. When performing pharmacovigilance duties in terms of working with data in adverse reaction reports, including the processing of patients' personal data or the primary sources of reports of adverse reactions, the requirements of the personal data protection legislation of the Member States shall be met. If the Member State's legislation does not allow the personal data transfer to the adverse reactions database by the MA holders or authorised authorities of the Member States during the processing of personal data shall ensure the use of coding (depersonalisation) with a change in personal data to aliases or codes following the applicable guidelines for the Rules of digital personal data in healthcare. Alternatively, to protect personal data when exchanging reports about adverse reactions in the E2B electronic data format, a special data masking system (*null Flavors*) can be used, with the help of which, for safety purposes, personal data becomes inaccessible to the recipient, but at the same time is not recorded as missing information.

539. MA holders or authorised authorities shall arrange application of personal data protection methods in the way that excludes any obstacles to the efficient and timely exchange and assessment of safety data. Given the high significance of such personal data as the patients' age or age group and gender, it is required that this part of personal data be stored in a visible and non-editable format.

24. The Use of Language When Presenting Individual Case Safety Reports

540. The submission of individual case safety reports in the pharmacovigilance system is based on the transfer of information in a structured and encoded electronic format, allowing processing, data synthesis, and signal detection. The scientific assessment of adverse reaction incidents and signal assessment requires a brief medical description of the adverse reactions in the reports.

541. Where MA holders submit individual case safety reports, the initial description of the adverse reaction by the primary source and the summary description of the adverse reaction shall be submitted as follows:

a) in Russian (or with the inclusion of a translation into Russian) if an adverse reaction is detected on the Member States territory;

b) in English if an adverse reaction has been detected in other countries.

542. When generating an individual case safety report in “Reaction (Event) in Accordance with the Source Description in the National Language” section, the original text describing the suspected adverse reaction by the source is retained, while in “Reaction (Event) in Accordance with the Source Description with Translation”, a translation of the original text describing the suspected adverse reaction by the primary source is presented in Russian in cases stipulated by paragraph 542 of these Rules. In the part of “Summary, Including a Clinical Description of the Case, Therapeutic Measures, Outcome, and Case Additional Information” section of E2B electronic data format a short description of the suspected adverse reaction is provided in Russian or English in accordance with paragraphs 540 and 541 of these Rules.

543. Where the reporter submits additional documents in any of the Member State’s national languages simultaneously with an individual case

safety report, the MA holder submits the translation into Russian when requested by the Member State's authorised authority.

25. Special Situations

Using Medicinal Products During Pregnancy and Lactation

544. When arranging work with reports of the medicinal product use during pregnancy and lactation, the general provisions of paragraphs 431–437 of these Rules shall be met.

545. When preparing individual reports of adverse reactions resulting from the medicinal product use during pregnancy or lactation, the provisions of paragraphs 546–549 of these Rules shall be met.

Development of a Suspected Adverse Reaction in a Child (Fetus), Except for Cases of Spontaneous Abortion in Early Pregnancy or Fetal Death

546. If a fetus or child exposed to one or more medicinal products as a result of their use by a parent develops one or more suspected adverse reactions, except for cases of spontaneous abortion in early pregnancy or antenatal death of a fetus, information on parent and child (fetus) shall be submitted in one individual report. In this case, it is a report for a parent and child (fetus). In the "Patient Characteristics" section of patient data, information on the child (fetus) is provided.

Data on the mother or father who caused the child (fetus) to be exposed to the suspected medicinal product shall be presented in a structured form in "Parent Information for Parent and Child (Fetus) Reporting Cases" section of E2B electronic data format. Where both of the parents were the cause of the impact on the child (fetus), information on the mother is presented in a structured form; information on the father is presented in summary along

with other information on the medical summary of the case in “Summary, Including a Clinical Description of the Case, Therapeutic Measures, Outcome, and Case Additional Information” section of E2B electronic data format.

Development of a Suspected Adverse Reaction in a Parent And Child (Fetus)

547. With the development of suspected adverse reactions (except for cases of spontaneous abortion in early pregnancy or antenatal death of a fetus), a parent and child (fetus) exposed to one or more medicinal products as a result of their use by a parent, two separate reports are formed about the development of an adverse reaction in a parent and child (fetus). To establish the relationship between reports for subsequent joint assessment, individual reports shall be assigned interrelated identification numbers using the data section “Identifier of an Individual Report Associated with this Report” of the individual case safety report in E2B electronic format.

No Adverse Reaction in a Child (Fetus)

548. If there is no adverse reaction in a child (fetus) who has been exposed to one or more medicinal products as a result of their use by a parent, the report about a parent and child (fetus) is not applicable. Regardless of taking one or more medicinal products, the parent forms an individual report on the parent as a patient, describing the intrauterine effects of the medicinal product on the child. The section “Patient Characteristics” includes data on the mother or father of the child (fetus). An individual report shall not be submitted if the parent has no adverse reaction due to using one or more medicinal products.

Report of Spontaneous Abortion in Early Pregnancy or Miscarriage

549. When an early spontaneous abortion or miscarriage is reported, an individual report is generated for the parent as a patient, with the mother's data included in "Patient Characteristics" section. Where the suspected medicinal product was taken by the father, the appropriately structured data element is selected to be included in the formed report in "Additional Information on the Medicinal Product" section of the individual case safety report in the E2B electronic format.

Adverse Reaction Reports Published
in the Scientific Medical Literature

550. When generating an individual report of an adverse reaction published in the scientific medical literature to be submitted electronically, a number of requirements should be taken into account:

a) the "Literature Source" section of E2B electronic data format shall be completed to include the numeric (discrete) subject identifier for the publication in the medical literature that was the source of the adverse reaction data;

b) detailed description of the adverse reaction case shall be included in "Summary, Including a Clinical Description of the Case, Therapeutic Measures, Outcome, and Case Additional Information" section;

c) at the authorised authority's request, if necessary to review safety information, the MA holder is provided with a copy of the relevant publication (considering the copyright protection legislation). A copy of the publication and a translation of the publication, if applicable, are included in the individual case safety report in "Attached Documents" section. If a copy of the publication is submitted separately from the previously submitted individual report, the originally submitted individual report with the included

additional document is resubmitted as part of the individual case safety report amendment procedure.

551. If a publication in the scientific medical literature includes a description of the development of cases of adverse reactions in several patients, an appropriate number of individual case safety reports is formed.

Reports of Adverse Reactions Due to Overdose, Development of Addiction, Use Not Following the Summary of Product Characteristics, Misuse, Medication Error, or Occupational Exposure

552. When reporting the development of adverse reactions due to overdose, the development of addiction, use not following the summary of product characteristics, misuse, medication error, or occupational exposure, the appropriate terms of the MedDRA dictionary shall be used to correctly reflect the nature of the effect of the medicinal product.

553. The general principles for reflecting the features of the medicinal product use in the E2B electronic data format include the following:

a) information on the suspected medicinal product in terms of the trade name and/or active ingredient is included based on the information provided by the source of the report about the adverse reaction with inclusion in the sections “Brand Name of the Medicinal Product” and “Name of the Active Ingredient”;

b) in “Additional Information on the Medicinal Product” section, structured data elements are selected that characterize the relevant exposure causes (e. g., overdose, misuse, medication error, development of addiction, occupational exposure, use not following the summary of product characteristics). The nature of the medicinal product’s effect is indicated in this section if the adverse reaction reporter did it. Where the source has not made a direct indication of overdose, the development of addiction, use not

following the summary of product characteristics, misuse, medication error, or occupational exposure, which can be transformed into the corresponding term of the MedDRA dictionary, though, this follows from the context of the clinical description of the adverse reaction, the reporter can select the most appropriate, in his/her opinion, structured data element characterizing the corresponding medicinal product effect and ensure subsequent collection of information and clarification of the assessment from the primary source of the adverse reaction;

c) in “Adverse Reaction (Event) in Accordance with MedDRA Terminology” section, appropriate lowest level terms shall be used to reflect the nature of the drug exposure and the adverse reaction (a set of adverse reactions) resulting from this exposure. Where applicable, based on the report assessment results, the reporter shall fill in the “Diagnosis (Syndrome) in the Reporter’s Opinion, Change in the Classification of a Reaction (Event)” section of the report form with the inclusion of appropriate justifications in the “Reporter Comments” section;

d) for a report about a medication error due to the patient’s erroneous receipt (provision, administration) of a medicinal product other than the prescribed one, the data item “Medicinal Product Not Prescribed” is selected in “Characterisation of the Role of the Medicinal Product” section, while the data on the prescribed product with indication of the fact that the medicinal product was not prescribed and the information on the wrongly prescribed product is provided in the “Medicinal Product Information” section.

Reports on Lack of Therapeutic Efficacy of Medicinal Products

554. When reporting a lack of therapeutic efficacy in “Adverse Reaction (Event) Following MedDRA Terminology” section, the lowest level terms of the MedDRA dictionary should be used that best reflects the original

description of the suspected lack of therapeutic efficacy provided by the primary source. A suspected medicinal product is included in "Adverse Reaction (Event)" if prescribed according to an indication for which the patient's condition is deteriorating. Requirements for urgent reporting (within 15 calendar days) of cases of lack of therapeutic efficacy apply, among others, to cases in which a suspected adverse reaction is not reported (e. g., for medicinal products used to treat life-threatening conditions, vaccines, contraceptives) and a reporter the patient's condition has not been identified as meeting the criteria for a serious adverse reaction.

Adverse Reaction Reports Arising from a Quality Defect in the Medicinal Product or the Use of Counterfeit Medicinal Products

Adverse Reaction Reports Arising from a Quality Defect in the Medicinal Product

555. When reporting adverse reactions associated with a suspected quality defect in a medicinal product, "Adverse Reaction (Event) Following MedDRA Terminology" should use the MedDRA dictionary's lowest level terms that best reflect the original description of the quality defect.

556. General principles for reporting adverse reaction information in the E2B electronic format include the following:

a) in addition to the obligatory "Name of the Medicinal Product According to the Primary Source Information" section, the "Information on Medicinal Products" section is completed following the information provided by the primary source and according to the guidelines for generating data on suspected, interacting and simultaneously prescribed medicinal products;

b) in "Additional Information on the Medicinal Product" section, a structured data element is selected if there is a corresponding unambiguous indication in the report of the primary source: "medicinal product after the

expiration date", "the quality control of the medicinal product series and batch confirmed compliance with the specification requirements", "the quality control of the medicinal product series and batch confirmed non-compliance with the specification requirements";

c) in "Adverse Reaction (Event) Following MedDRA Terminology" section appropriate lowest level terms shall be used to reflect the characteristics of the medicinal product and the adverse reaction (a set of adverse reactions) resulting from the use of a product with a suspected quality defect. Where applicable, according to the results of the report assessment, the reporter shall fill in the "Diagnosis (Syndrome) in the Opinion of a Reporter, Change in the Classification of a Reaction (Event)" section of the report form with the inclusion of appropriate justifications in the "Reporter Comments" section.

d) additional comments on the medicinal product in text form are included in "Additional Information on the Medicinal Product" section.

Reports of Adverse Reactions Arising from the Use of a Counterfeit Medicinal Product

557. When reporting adverse reactions arising from the use of a medicinal product, for which the fact of counterfeiting the active ingredients, excipients, or the product in general is suspected or confirmed, the MedDRA lowest level terms should be used in the "Adverse Reaction (Event) Following MedDRA Terminology" section to most accurately reflect the information on the counterfeit product provided by the primary source.

558. General principles for reporting adverse reaction information in the E2B electronic format include the following:

a) in addition to the obligatory "Name of the Medicinal Product According to the Primary Source Information" section, the section

“Information on Medicinal Products” is completed following the information provided by the primary source of the report and according to the recommendations for generating data on suspected, interacting and simultaneously prescribed medicinal products;

b) where the use of a counterfeit medicinal product is suspected or confirmed, the structured data element “Counterfeit” is selected in the “Additional information about the drug” section;

c) appropriate lowest level terms shall be used in the “Adverse Reaction (Event) Following MedDRA Terminology” section to reflect the characteristics of the medicinal product and the adverse reaction (a set of adverse reactions) resulting from the use of a product for which the counterfeiting is suspected or confirmed. Where applicable, based on the report assessment results, the reporter shall fill in the “Diagnosis (Syndrome) in the Reporter’s Opinion, Change in the Classification of a Reaction (Event)” section of the report form with the inclusion of appropriate justifications in the “Reporter Comments” section;

d) additional comments on the medicinal product in text form are included in “Additional Information on the Medicinal Product” section.

Reports of Suspected Transmission of an Infectious Agent Due to a Medicinal Product Use

559. When reporting adverse reactions associated with suspected transmission of an infectious agent due to a medicinal product use, the “Adverse Reaction (Event) Following MedDRA Terminology” section should use the MedDRA dictionary’s lowest level terms that best reflect the information regarding the infectious agent from the primary source of the report.

Suspected Adverse Reaction Reports from Organised Data Collection Systems

560. General provisions for data management of individual case safety reports received during post-authorisation studies (interventional clinical trials and non-interventional studies) are defined in paragraphs 468–473 of these Rules. When generating individual reports of adverse reactions detected during these studies in the electronic E2B data format, the “Study Identification” section should include information on the study type, study name, study number assigned by the sponsor, and study registration number.

561. Provisions for managing individual case safety reports received from patient support programs or marketing study programs are defined in paragraph 475 of these Rules.

562. The following recommendations should be considered when generating individual case safety reports from organised data collection programs:

a) when generating adverse reaction reports for which the protocol of the non-interventional post-authorisation study determines the performance of a systematic data collection, or where the compassionate use or personalised use program provides for an active collection of safety data, or in case reports are received as a result of implementing patients or market study support programs, adverse reaction reports are considered solicited ones and the data item “Report Received During Study” is selected in “Report Type” section if a relationship between the investigational product and an adverse reaction is suspected. In the “Type of Study where an Adverse Reaction was Detected” section the appropriate data item “Other Studies” or “Individual Use by a Patient” is selected. Where it is assumed that there is a relationship between the adverse reaction and the medicinal product that is not the object of the study and is not supposed to be the cause of the

undesirable role of the interaction with the investigational medicinal product, the data item “Spontaneous Report” is selected in the “Report Type” section.

b) when generating adverse reaction reports for which the protocol of the non-interventional post-authorisation study does not specify the performance of systematic data collection, or where a compassionate use program or a personalised use program that does not provide for the active safety data collection, the adverse reaction reports are considered spontaneous reports, and the “Spontaneous Report” data item is selected in the “Report Type” section if a relationship between the investigational product and the adverse reaction is suspected.

c) when generating a report of adverse reaction received during an interventional clinical study, for which a relationship with a medicinal product other than the investigational product is assumed, and the role of the interaction with the investigational product is not assumed as the cause of the adverse reaction, the adverse reaction reports are considered spontaneous ones and the data item “Spontaneous Report” is selected in “Reporter Type” section.

26. Obtaining Minimal Missing Information

563. When receiving minimal missing information regarding a previously invalid individual case safety report, the following data entry guidelines should be followed:

a) the date in “Date of Initial Report Received from Reporter” section shall reflect the date of receipt of the initial invalid individual case safety report;

b) the date in “Date of Last Report Information Received” section shall reflect the date the minimum missing information was received to ensure that the criteria for the validity of individual case safety reports were met;

c) the “Summary, Including a Clinical Description of the Case, Therapeutic Measures, Outcome, and Case Additional Information” section should indicate which of the four elements of minimum information about an adverse reaction was missing from the original report;

d) a compliance assessment shall be performed on each date of obtaining additional information.

27. The Electronic Data Quality in an Individual Case Safety Report and the Management of Duplicate Adverse Reaction Reports

564. Member States’ databases of adverse reactions shall contain all cases of suspected adverse reactions to be reported in accordance with the requirements of these Rules. When submitting individual case safety reports to the Member States databases, it shall be ensured that the requirements of these Rules for the electronic data format, structuring, and coding of information are met. The Member States’ authorised authorities of and MA holders are responsible for the following:

a) implementing a set of procedures to ensure a high level of quality and integrity of information on adverse reactions submitted to the Member States’ adverse reactions database;

b) ensuring proper monitoring of the terminology compliance with the terminology requirements through systematic assessment of data on adverse reactions in the database or through regular assessment of a random sample;

c) compliance with the requirements for the quality, reliability of the information, and the time to submit reports of adverse reactions to the Member States’ authorised authorities;

d) compliance with the requirements for the quality, integrity, completeness of reports of adverse reactions in accordance with the requirements for their structure, format and content.

e) performing procedures for managing duplicate adverse reaction reports.

565. To confirm compliance of the pharmacovigilance quality system with the requirements for arranging the work with duplicate reports, including the identification and management of duplicate messages and fulfillment of immediate reporting requirements, the MA holders and the Member States' authorised authorities shall ensure that regular and risk-based audits of the quality system are carried out. Should any non-compliance of the quality system with the established requirements be detected, corrective actions shall be taken, including subsequent audits. The dates and results of all audits shall be documented in accordance with the provisions of Section V of these Rules.

566. Following the requirements for maintaining and improving the pharmacovigilance quality system, MA holders and authorised authorities must ensure a sufficient number of qualified and trained personnel to carry out pharmacovigilance activities. Professionals involved in pharmacovigilance activities shall undergo initial and periodic follow-up training in accordance with their roles and responsibilities. To document, maintain, and develop personnel competencies, it is required to formulate a training plan and reports, available for assessment during audits or pharmacovigilance system inspections.

567. The Member States' authorised authorities regularly assess the quality and completeness of individual case safety reports submitted by MA holders and compliance with the requirements for submitting adverse reaction reports. Based on the assessment results, the MA holders can be sent reports, including, in the event of inconsistencies, recommendations on corrective actions and the time frame for their implementation. The way corrective action is taken and the recommended time frame for completion depends on

the identified quality system inconsistency (e. g., adjustments to the MedDRA terminology code used in an individual report can be made by submitting changes to a previously submitted report).

568. MA holders and the authorised authorities shall work together to manage duplicate reports in such a way as to ensure that potential duplicate adverse reactions are identified, evaluated, acknowledged, and processed.

28. Electronic Exchange of Adverse Reaction Data Between Multiple Reporters and Recipients

569. The need to exchange adverse reaction data electronically between multiple reporters or recipients may be related to the MA holders' contractual obligations or other features of the organisation of adverse reaction data collection processes.

570. The procedures for the adverse reaction data exchange shall be organised and carried out so that during the exchange, the adverse reaction information is not lost or changed unless new data on the corresponding adverse reaction becomes available to the party participating in the transmission of the individual report.

571. To improve the quality of the submitted adverse reaction reports, if the reporter reveals errors or inconsistencies in the report, the reporter should contact the report's source to ensure that the initial report appropriate adjustments are made. If it is impossible to correct the primary report within the time period established by the requirements for submitting adverse reaction reports, the reporter can make changes independently in terms of correcting the incorrect data structuring.

572. At all stages of the electronic adverse reaction data exchange, the E2B electronic data format requirements for providing follow-up adverse reaction information shall be met. Failure to comply with these requirements

creates the risk of disrupting the electronic adverse reaction data management system and contributes to duplicating reports in the recipient’s adverse reactions database.

29. Cooperation with the World Health Organisation

573. The authorised authorities ensure the regular submission of individual reports on detected and suspected adverse drug reactions in their territories to the World Health Organisation collaborating center to include information about these cases in the World Health Organisation adverse reactions database.

VIII. Periodic Safety Update Reports

574. The Periodic Safety Update Report (PSUR) is a pharmacovigilance document that allows the MA holder to provide an assessment of the risk–benefit ratio of a medicinal product at certain stages of the post-authorisation period.

575. The authorised authorities of the Member States shall assess the periodic safety update report with the establishment of possible new identified risks and their impact on the assessment of the risk–benefit ratio of a medicinal product. Based on the results of the assessment of the periodic safety update report, the Member State’s authorised authority determines the need for further safety or efficacy studies of a medicinal product, the use of certain actions concerning the authorisation status of a medicinal product, or changes in the summary of product characteristics to ensure product use when benefits overweigh risks.

1. Objectives of the Periodic Safety Update Report

576. The main objective of the periodic safety update report is to provide a comprehensive and critical analysis of a medicinal product's risk–benefit ratio, considering all-new safety data and the cumulative impact of these safety and efficacy data of a medicinal product. A periodic safety update report is a tool for post-authorisation assessment of the risk–benefit ratio of a medicinal product at certain stages of its life cycle.

577. The periodic safety update report is not intended to immediately provide important safety or efficacy information, nor is it a tool to identify new safety information. Performing a cumulative assessment of safety and efficacy data in a periodic safety update report may lead to identifying new aspects of the safety profile or efficacy of a medicinal product.

578. The MA holder shall constantly assess and analyze the impact of new data on the risk–benefit ratio, re-assess this indicator, and determine the need to optimize the risk–benefit ratio by introducing effective risk management measures and their minimisation when new safety information on a medicinal product during its post-authorisation use is identified.

Principles for Assessing the Risk–Benefit Ratio in the Periodic Safety Update Report

579. Assessment of the risk–benefit ratio shall be continuous throughout a medicinal product's entire life cycle to protect public health and improve the level of patient safety by implementing effective risk minimisation measures. Safety and efficacy Information for a medicinal product collected over appropriate periods of time, constituting the reporting periods, is the basis for such an assessment and analysis.

580. The risk assessment is based on information on all aspects of medicinal product use, including long-term use of the medicinal products,

application features in real medical practice, use not following the summary of product characteristics or package inserts, use in special populations. Sources of information regarding the results of use not following the summary of product characteristics or package insert include data on assessing the use of the medicinal product in real medical practice, spontaneous reporting data, and publications in the scientific medical literature. The assessment of benefits is based on the results obtained in clinical trials and the results of use in real medical practice for approved indications. An integrated assessment of the risk–benefit ratio shall be performed for each of the approved indications and shall consider the risks associated with the use of the medicinal product, not following the summary of product characteristics or the package insert.

581. The assessment includes the following stages:

a) critical analysis of all safety information received during the reporting period, identifying possible identified new signals indicating new potential or identified risks, or supplementing the existing knowledge on previously identified risks;

b) critical generalisation of all safety and efficacy information received during the reporting period for a medicinal product (both in clinical trials and in the use of the medicinal product in medical practice) and assessment of the impact of this information on the medicinal product’s risk–benefit ratio;

c) performing an integral analysis of the risk–benefit ratio based on all cumulative data starting from the medicinal product birth date or the date of the first approval to conduct an interventional clinical study in any of the states. Where the date of the first approval to conduct an interventional clinical study is unavailable or a MA holder does not have access to data on the clinical development of a medicinal product, the earliest available period

for starting the use of the medicinal product can be used as an initial stage for subsequent inclusion and assessment of cumulative data;

d) summarizing information on risk minimisation measures that may have been carried out during the reporting period and planned risk minimisation measures;

e) determining a plan for assessing signals, risks, and/or proposals for additional pharmacovigilance activities.

3. The Principle of Preparing a Periodic Safety Update Report

582. The MA holder shall prepare a single periodic safety update report for all manufactured medicinal products containing the same active ingredient or the same combination of active ingredients for all approved indications for these medicinal products, routes of administration, dosage forms, and dosage regimens. In special cases, it may be necessary to present data for individual indications, dosage forms, modes of administration, or dosage regimes as a separate section of a periodic safety update report with appropriate description and analysis of aspects of the safety profile and without preparing a separate periodic safety update report. The preparation of a separate periodic safety update report may be justified in exceptional cases (e. g., if there is a formulation with indications for the medical use of this product completely different from dosage forms) in agreement with the authorised authority.

4. Reference Information

583. The following sources of reference information can be used by the MA holder as reference information on a medicinal product:

A list of basic data on a MA holder’s medicinal product, including safety data, indications, dosage regimen, pharmacological properties, and other information regarding the medicinal product. Safety information included in the list of basic data on a medicinal product is defined as the company core safety information. When preparing a periodic safety update report, the current version of the list of basic data for a medicinal product, which is closest to the end of the reporting period of the document, can be used as a reference safety information and the main approved indications when performing the medicinal product’s risk and benefit assessments. Where the list of product core safety information does not include information on approved indications, the MA holder may determine and indicate another document used for this section of reference information;

If the MA holder does not have a list of core data on the medicinal product or product core safety information (e. g., if the medicinal product is authorised only in one state or region, or if a generic or well-studied medicinal product has been used for a large number of years), the MA holder may identify and specify another document that was used as reference information in the preparation of the periodic safety update report. In this case, the summary of product characteristics approved by the Member State’s authorised authority can be used as reference information. Where the reference information on approved indications for use is a separate document from the reference safety information, the current version of this document closest to the end of the reporting period shall be included in the periodic safety update report as an annex.

584. The MA holder shall constantly assess the need to revise the reference information for a medicinal product and/or reference safety information in connection with the receipt of new safety information to ensure the timely introduction of significant changes that occurred during the

reporting period and described in Section 4 “Changes Made to the Reference Safety Information of the Medicinal Product” and, if applicable, in Section 16 “Signals and Risk Assessment” of the periodic safety update report. These significant changes may include the following:

a) changes in the sections “Contraindications”, “Special Instructions and Precautions for Use”;

b) supplements to the sections “Adverse Reactions”, “Drug Interaction and Other Types of Interaction”;

c) supplementing with important new information to the “Overdose” section;

d) exclusion of indications, or other restrictions on the use of the medicinal product, introduced based on its safety data or insufficient therapeutic efficacy.

585. The MA holder shall submit copies of all versions of the reference information for a medicinal product in force at the end of the reporting period (e. g., for different dosage forms of a medicinal product included in one periodic safety update report) as annexes to the periodic safety update report. Versions of the reference information for a medicinal product shall have an effective date and are subject to the MA holder’s control.

586. In case of receiving important safety information requiring to make changes to the current reference information of the medicinal product, after the data lock point before submitting the periodic safety update report to the Member State’s authorised authority, this information shall be included in Section 14 “Important Information Received on Completion of the Periodic Safety Update Report Preparation,” if possible.

5. Contents of the Periodic Safety Update Report

587. The periodic safety update report should include cumulative data from the medicinal product birth date and highlight new information received during the reporting period. Cumulative information is considered when conducting an overall safety assessment of a medicinal product and an integrated assessment of its risk–benefit ratio.

588. Since a medicinal product's clinical development may continue at the post-authorisation stage, the periodic safety update report shall include data from post-authorisation or clinical trials on unapproved indications or unapproved populations. Safety data on a medicinal product obtained from the results of use not following the summary of product characteristics or package insert shall also be included in assessing the relevant risks in a periodic safety update report applicable and justified.

589. A periodic safety update report shall include summarizing information on all sources of significant data on the medicinal product's efficacy and safety, which shall be considered when performing the next assessment of the risk–benefit ratio and which are available to the MA holder. Sources of data on the medicinal product safety and efficacy that can be used when preparing a periodic safety update report shall include:

a) preclinical trials (toxicological and *in vitro* studies);

b) spontaneous reporting;

c) active monitoring methods (e. g., analysis of internal or external databases);

d) medicinal product quality studies;

e) studies to assess the use of a medicinal product;

f) clinical trials, including studies on disapproved indications;

g) observational studies, including registries;

h) patient support programs;

i) data from systematic reviews and meta-analyses;

j) MA holder’s websites on the Internet;

k) published data from medical and scientific literature or abstracts of articles, including information presented at scientific conferences and meetings;

l) unpublished manuscripts;

m) data from licensing partners, other sponsors, or scientific and research institutions;

n) data from the authorised authorities (all states of the world).

590. The list of information sources is not exhaustive; the MA holder can use additional data sources to provide safety and efficacy information in a periodic safety update report to assess the risk–benefit ratio, properly and correctly reflect important safety and efficacy aspects of a medicinal product, known and identified during the reporting period. The MA holder shall provide the list of sources of information used to prepare the periodic safety update report in an annex to the document.

591. The periodic safety update report shall be developed in the form of a document consisting of sections determined in paragraph 590 of these Rules. Requirements for sections are common to all MA holders. The volume of data submission by section may vary depending on the different levels of access of MA holders to information sources included in a periodic safety update report. For example, the MA holder who sponsored a clinical study can access the full body of patient-level data. In contrast, other MA holders who did not sponsor the clinical study may only have access to published data.

592. The level of detail of the information provided in certain sections of the periodic safety update report shall be determined following the

important safety and efficacy aspects known and identified during the reporting period, which constitute the key components of assessing the risk–benefit ratio of the medicinal product.

593. A periodic safety update report shall include the following sections:

Part I. Title Page, including a signature of the person responsible for preparing the periodic safety update report

Part II. Summary (abstract)

Part III. Contents of the Periodic Safety Update Report

Section 1. Introduction

Section 2. Global Authorisation Status of the Medicinal Product

Section 3. Measures Taken in the Reporting Period in Connection with the Received Data on the Medicinal Product Safety

Section 4. Changes Made to the Reference Safety Information of the Medicinal Product

Section 5. Estimating the Number of Patients Exposed to a Medicinal Product and the Features of Its Use in Medical Practice

Subsection 5.1. Total Number of Patients Exposed to the Medicinal Product in Clinical Trials

Subsection 5.2. Total Number of Patients Exposed to the Medicinal Product According to Market Data on Its Use

Section 6. Summarised Tabular Data

Subsection 6.1. Reference Information

Subsection 6.2. Summarised Information on Serious Adverse Events Detected in Clinical Trials

Subsection 6.2. Summarised Information on the Medicinal Product Post-Authorisation Use Data

Section 7. Summary of Significant Data Obtained from Clinical Trials in the Reporting Period

Subsection 7.1. Completed Clinical Trials

Subsection 7.2. Ongoing Clinical Trials

Subsection 7.3. Long-term Follow-Up Monitoring of Patients' Conditions

Subsection 7.4. Other Therapeutic Use of the Medicinal Product

Subsection 7.5. New Safety Data on the Fixed-Dose Combination Medicinal Product in Use

Section 8. Data from Non-Interventional Studies

Section 9. Data from Other Clinical Trials and Data Obtained from Other Sources

Subsection 9.1. Data from Other Clinical Trials

Subsection 9.2. Medication Errors

Section 10. Data from Preclinical (Non-Clinical) Studies

Section 11. Data from the Scientific Medical Literature

Section 12. Other Periodic Safety Update Reports

Section 13. Insufficient Therapeutic Efficacy of the Medicinal Product Established in Controlled Clinical Trials

Section 14. Important Information Received on Completion of the Periodic Safety Update Report Preparation

Section 15. Overview of Signals (New, Pending and Closed)

Section 16. Signals and Risk Assessment

Subsection 16.1 Summary of Safety Concerns

Subsection 16.2. Signal Assessment

Subsection 16.3. Assessment of Risks and New Information

Subsection 16.4. Risk Characteristics

Subsection 16.5. Effectiveness of Risk Minimisation Measures (where applicable)

Section 17. Benefit Assessment

Subsection 17.1. Important Core Efficacy Information on the Medicinal Product

Subsection 17.2. Newly Identified Efficacy Information

Subsection 17.3. Benefit Characteristics

Section 18. Integrated Risk-Benefit Ratio Analysis For Approved Indications

Subsection 18.1. Integrated Analysis in the Context of the Risk–Benefit Ratio (Including the Medical Need and Important Alternatives)

Subsection 18.2. Assessment of the Procedure for Analyzing the Risk–Benefit Ratio

Section 19. Conclusion of the Periodic Safety Update Report and Suggested Follow-Up Actions

Section 20. Annexes to the Periodic Safety Update Report

Part I Title Page

594. The title page shall contain the following information:

name of the medicinal product and active ingredient:

international date of the medicinal product authorisation;

reporting period;

report date;

data on the marketing authorisation holder;

an indication of the confidentiality of information included in the periodic safety update report.

The title page of the periodic safety update report shall be signed by an authorised pharmacovigilance officer or a person who has been delegated the function of approving the periodic safety update report.

If a marketing authorisation holder does not have information about the actual international birth date of the medicinal product, it is necessary to refer to the lists of published international birth dates. If the medicinal product is not included in any list, a marketing authorisation holder should agree with the authorised authority on the possibility of using the first known birth date of receipt of the marketing authorisation for the active ingredient as the international birth date.

Part II. Summary (abstract)

595. The purpose of the specified structural element of the periodic safety update report is a concise summary of the content and the most important information that makes up the specified report. The summary shall include the following information:

a) introduction, indication of the reporting period;

b) medicinal product name, pharmacotherapeutic class, mode of action, indications, dosage form, strength(s), route(s) of administration;

c) assessment of cumulative impact in clinical trials;

d) assessment of the interval of post-authorisation application and cumulative impact for this post-authorisation period;

e) the number of states in whose territories the use of the medicinal product is permitted;

f) summarised information on the assessment of the risk–benefit ratio;

g) taken and proposed actions related to the safety aspects, including significant changes made to the investigator’s brochure at the clinical trials stage

and the summary of product characteristics at the post-authorisation stage or other risk minimisation measures;

h) conclusion.

6. Requirements for the Content of Each Section of the Periodic Safety Update Report

Part III. Contents of the Periodic Safety Update Report

596. The summary (abstract) shall be supported by a table of contents of the periodic safety update report.

Section 1. Introduction

597. The introduction shall contain the following information:

a) international birth date and reporting period;

b) medicinal product name, pharmacotherapeutic group, mode of action, approved indications, dosage form(s), strength(s), route(s) of administration;

c) a summary of the populations receiving prescription drug treatment and included in clinical trials.

Section 2. Global Authorisation Status of the Medicinal Product

598. This section shall provide the following brief overview:

a) birth date in any state of the world;

b) approved therapeutic indications;

c) authorised forms of release and dosage;

d) indication of the states in which the medicinal product is authorised.

Section 3. Measures Taken in the Reporting Period in Connection with the Safety Data on the Medicinal Product

599. This section provides a description of the significant measures taken by the authorised authorities, the MA holder, the sponsor of clinical trials, the data monitoring and evaluation committee, the ethics committee based on safety data for the reporting period, both concerning ongoing clinical trials and post-authorisation applications. These measures include steps that:

had a significant impact on the risk–benefit ratio of the authorised medicinal product;

impacted the conduct of a particular clinical trial or the overall clinical development program for a medicinal product.

The section shall indicate the grounds for taking these measures and additional information (if any). This part also provides a summary of how to update the status of previously adopted measures.

600. Significant actions taken concerning the investigational medicinal product may include:

a) refusal to approve the clinical study due to safety or ethical issues;

b) partial or complete suspension of a clinical study or a complete early termination of a clinical study due to detected safety data or insufficient therapeutic efficacy;

c) recall of the investigational product or reference product;

d) refusal to issue a permit for use according to an indication investigated in the course of a clinical study, including a voluntary refusal to apply for a marketing authorisation;

e) risk minimisation measures, including:

changes made to the study protocol and data on medicinal product safety or efficacy (e. g., changing the dosage regimen, changing the criteria for

inclusion in or exclusion from a clinical study, introducing additional monitoring measures for study subjects, limiting the study duration);

study population restrictions or indications:

informed consent changes due to safety profile aspects;

change in the medicinal product composition;

an additional requirement of the Member States' authorised authorities on a special procedure for submitting a medicinal product's safety information;

special information to medical investigators or medical professionals;

planning new studies to assess safety aspects.

601. Significant measures taken concerning the authorised medicinal product include:

a) refusal to renew the marketing authorisation;

b) suspension or withdrawal of marketing authorisation;

c) measures taken in connection with identifying a quality defect or other quality-related reasons concerning the medicinal product;

d) introduction of a risk minimisation plan, including:

significant restrictions in the distribution or the introduction of other risk minimisation measures;

significant changes in the summary of product characteristics, including restrictions on indications for prescription or groups of patients to whom the medicinal product is prescribed;

special healthcare professional communication;

the requirement of the Member States' authorised authorities to conduct a post-authorisation study.

Section 4. Changes Made to the Reference Safety Information of the Medicinal Product

602. This section indicates information on all significant changes made to the reference safety information of the medicinal product during the reporting period. These significant changes include:

changes to sections of contraindications, cautions, and special instructions;

information on serious adverse reactions, adverse reactions of particular interest and reactions of interaction;

important data from ongoing and completed clinical trials;

important data from preclinical (non-clinical) studies (for example, carcinogenicity studies).

Information on these changes shall be presented in the appropriate sections of the periodic safety update report. An annex to the periodic safety update report shall contain the version of the reference safety information of a medicinal product with the appropriate changes.

Section 5. Estimating the Number of Patients Exposed to a Medicinal Product and the Features of Its Use in Medical Practice

603. A periodic safety update report shall contain an accurate estimate of the number of patients who have been exposed to a medicinal product, including all data on sales and prescriptions. This assessment shall be accompanied by a qualitative and quantitative analysis of the medicinal product use in real medical practice, indicating how this may differ from the approved use, based on all the data available to a MA holder and the results of observational studies assessing the use of a medicinal product.

604. This section shall assess the size and characteristics of the population exposed to the medicinal product (including a short description of the method used for the assessment and an indication of the method limits).

605. Consistent methods for assessing subject or patient exposure shall be used in all sections of a periodic safety update report for a single medicinal product. Where it is appropriate to change the assessment method used, the method used and the new method, as well as the calculations thereto, shall be presented in a periodic safety update report with the replacement explained.

Subsection 5.1. Total Number of Patients Exposed to the Medicinal Product in Clinical Trials

606. This subsection of the periodic safety update report shall contain the following information about patients included in clinical trials sponsored by the MA holder (a tabular format is recommended):

a) the cumulative number of study subjects included in ongoing and completed clinical trials and exposed to the investigational product, placebo, and/or active comparison product since the development international birth date. For medicinal products that have been in circulation for a long time, the specified detailed information may not be available.

b) more detailed cumulative information about the study subjects exposed to the medicinal product (if any) (e. g., cumulative information grouped by age, gender, race throughout the development program);

c) important differences between studies concerning the prescribed doses, routes of the medicinal product administration, patient subgroups:

d) where clinical trials were carried out on special groups of patients (e. g., pregnant women, patients with impaired renal, liver, cardiovascular system, and clinically significant genetic polymorphism);

e) exposure assessment expressed as subject-time indicators (patient-days, -months or -years) (where there are significant differences in the time of exposure to the medicinal product between the subjects randomised to receive the investigational medicinal product or comparator, or where there are inconsistencies in duration of exposure between clinical trials);

f) data on the effect of the investigational product in healthy volunteers may be of less value for assessing the medicinal product's safety profile in general, depending on the type of adverse reactions observed, especially if patients are exposed to a single dose (to be presented separately and, where necessary, with explanations);

g) guidelines for assessing the medicinal product's effect on the patient (if the generalised information on adverse reactions detected in clinical trials contains data on serious adverse reactions);

h) patients' demographic characteristics for particular especially important clinical trials (to be submitted separately from the information specified in subparagraphs "a"–"g" of this paragraph).

Subsection 5.2. Total Number of Patients Exposed to the Medicinal Product According to Market Data on its Use

607. This Subsection, whenever possible, shall include a separate assessment of the cumulative impact (from the international birth date) and the medicinal product effect within a particular interval (from the lock point for data on the previous periodic safety update report). The section shall estimate the number of patients exposed to the medicinal product and how the determination and assessment were performed.

Where it is impossible to calculate the number of exposed patients, a justification shall be provided. Where it is not possible to estimate the number of patients, alternative estimates shall be presented to indicate how they were

performed. Alternative indicators of exposure assessment are patient-days and the number of prescriptions. Only in cases where these indicators are not available, sales estimates expressed in weight units or doses can be used. The concept of the Defined Daily Dose (DDD) can be applied to obtain patient exposure data.

608. Exposure data shall be given for the following categories of its use:

a) post-authorisation use (except for clinical trials). In this case, an overall assessment shall be given with data broken down by gender, age, indication, strength, dosage form, and region, where applicable. Depending on a medicinal product, other variables may be listed as significant (e. g., number of vaccinations performed, route of administration, and duration of treatment). Should a series of adverse reaction reports suggesting a signal be detected, data on exposure of the relevant subgroup of patients to the medicinal product shall be provided where possible;

b) post-authorisation use in special population groups. Where the medicinal product is used in special populations in the post-authorisation phase, available information on the cumulative number of patients exposed and the used calculation method shall be provided. Sources of this data may include non-interventional studies designed specifically to generate data for specific population subgroups, including patient registries. Other sources of information may include collecting data on adverse reactions outside of clinical trials using a spontaneous reporting system (e. g., the section may provide information on exposure during pregnancy without the development of an adverse reaction). Populations included in the assessment under this section include but are not limited to:

pediatric population;

elderly population;

women during pregnancy and lactation;

patients with impaired liver and/or kidney function;

patients with other important comorbidities;

patients whose disease severity differs from that investigated in the clinical trials;

subpopulations with a carrier of genetic polymorphism(-s);

patients with a different (not studied in clinical trials) race or ethnicity;

c) features of the medicinal product use.

609. Where a MA holder becomes aware of certain features of using a medicinal product, a description of these features shall be provided. An appropriate assessment and interpretation of safety data shall be made. These features include, in particular, overdose, development of addiction, misuse, use of the drug in medical practice for indications not included in the approved list (e. g., the use of an antiepileptic drug for the relief of neuropathic pain or the prevention of migraine headache).

610. Should the information on the medicinal product use features, which were not accompanied by adverse reactions, be necessary to assess the risk–benefit ratio of the medicinal product, it can be summarised in this part of the section. This information may be obtained from spontaneous reports, requests for medical data, consumer complaints, digital media assessments, and other sources available to the MA holder.

611. The section provides data that make it possible to make a quantitative assessment of the medicinal product use features in medical practice (if any). If relevant data is available, the MA holder can comment on the extent to which the use is supported by clinical protocols, the evidence base for clinical trials, or the lack of generally authorised alternatives.

612. When determining aspects of the use of a medicinal product that do not correspond to the reference information, the marketing authorisation holder shall use the version of the relevant section of the reference information valid as

of the end of the reporting period of the specified report (e. g., approved indications, route of administration, contraindications).

Section 6. Summarised Tabular Data

613. The purpose of this section is to present data on serious adverse reactions and events identified in clinical trials, as well as at the stage of post-authorisation use, in the form of summarised tabular data. Post-authorisation data may include spontaneous adverse reaction reports (including reports from healthcare professionals, consumers), publications in the scientific medical literature, data from authorised pharmacovigilance authorities of the countries of the world, as well as data obtained during non-interventional studies and other organised data collection programs. The MA holder may display certain aspects of the data in graphical form to facilitate perception and understanding.

614. Data on adverse reactions in a summarised tabular form are presented using MedDRA terminology at the level of preferred terms and system organ classes.

615. The classification of adverse reactions as serious adverse reactions in the summarised tabular data shall comply with the seriousness criteria established by the terminology of these Rules. Where an individual report of an adverse reaction includes serious and non-serious adverse reactions, in the summarised tabular data, an indication of the severity is made individually for each reaction. The assessment of seriousness shall not be changed when preparing data for inclusion in the periodic safety update report.

Subsection 6.1. Reference Information

616. This subsection specifies the version of the dictionary used to represent adverse events and reactions.

Subsection 6.2. Summarised Information on Serious Adverse Events Detected in Clinical Trials

617. This subsection shall provide the justification for the annex to the periodic safety update report, which includes cumulative summarised tabular data on serious adverse events that have been identified in clinical trials organised by a MA holder, starting from the development international birth date until the data lock point for the current periodic safety update report. The MA holder shall explain all excluded data (e. g., data from clinical study results may not be available for several years). According to the MedDRA dictionary, data in tabular form shall be grouped according to the classification of adverse reactions by system organ classes for the investigational medicinal product and comparators (active and placebo). When appropriate, data can be grouped by clinical trial, indication, administration route, and other variables.

618. When working with certain types of data presented in this subsection, the following should be taken into account:

a) providing information on causal link is important when assessing rare adverse reactions. The data on the causal link for individual cases of adverse reactions are less significant when assessing the aggregated data, which allow comparison of the incidence between the comparison groups. On this basis, the summary information should provide data on all serious and other adverse events and reactions for the investigational medicinal product and the comparators (active and placebo) so that it is possible to make group comparisons, including in terms of frequency. It is expedient to present data showing the relationship between a dose and frequency of adverse reactions.

b) the summarised tabular data on serious adverse events identified in the clinical study includes terms that have been determined to meet the criteria for a serious adverse event. Information on adverse events that do not meet the seriousness criteria is included in the clinical study report;

c) the summarised tabular data shall include both blinded and unblinded data on serious adverse events in clinical trials. Unblinded data may be reported from completed clinical trials and individual case studies that have been blinded for specific reasons (e. g., safety considerations or to meet urgent reporting requirements). Clinical study sponsors and MA holders do not perform unblinding directly in connection with preparing a periodic safety update report.

d) certain adverse reactions can be excluded from the summarised information, but all such exclusions shall be justified in a periodic safety update report. For example, adverse reactions identified in the protocol as excluded from the special collection and urgent reporting procedure and only included in the general database because they are inherent in the target population or coincide with endpoints can be excluded from the summary information.

Subsection 6.3. Summarised Information on the Medicinal Product Post-Authorisation Use Data

619. This section provides a justification for the annex, which cumulatively includes summarised tabular data on adverse reactions for the entire period and the reporting period, from the international birth date of a medicinal product until the data lock point. The annex also contains information on adverse reactions obtained in non-interventional studies and spontaneous reporting, including data from medical and pharmaceutical professionals, consumers, patients, the Member States' authorised authorities, and data published in the medical literature. Serious and non-serious adverse reactions from spontaneous reporting, as well as serious adverse reactions from non-

interventional studies and other non-interventional data collection programs, shall be reported in one table. The data in the table shall be distributed according to the MedDRA classification by organ function classes. For critical safety profile aspects, separate tables of adverse reactions can be presented where the data is grouped according to indications, route of administration, and other parameters.

Section 7. Summary of Significant Data Obtained from Clinical Trials During the Reporting Period

620. This section should provide a summary assessment of the clinically important data on the medicinal product's efficacy and safety identified during the reporting period when the MA holder conducted clinical trials. Where possible, data should be categorised by gender and age (especially adult and pediatric populations), indication, dosage regimens, and regions.

621. Signals identified during clinical trials shall be tabulated in Section 15 of the Periodic Safety Update Report "Signal Review: New, Pending or Closed." A description of the procedure and results of the evaluation of signals completed in the reporting period with the rationale of their subsequent classification as rejected signals or potential or identified risks is included in Section 16.2 "Signal Assessment" of the periodic safety update report. New information on previously known potential or identified risks, which is not assessed as a newly identified signal, is reflected in Sections 16.3 "Assessment of Risks and New Information" and 16.4 "Risk Characteristics" of the periodic safety update report.

622. Safety and efficacy data from clinical trials where the marketing authorisation holder was not a sponsor is reported in other relevant sections of the periodic safety update report. This section provides summarised information from clinical trials on the lack of therapeutic efficacy when prescribed for

approved indications to treat life-threatening diseases. Clinical study evidence of lack of efficacy in the treatment or prevention of serious or life-threatening disease should be reported in Section 13 of "Insufficient Therapeutic Efficacy in Controlled Clinical Trials" of the periodic safety update report.

623. In an annex to this section, a MA holder shall enumerate the interventional clinical trials arranged by him/her, which were completed or continue to be performed during the reporting period, to be able to identify, characterize and quantify the level of risks or to confirm the safety profile of the medicinal product, indicating the following information on each study:

a) clinical study identifier (e. g., study protocol number or another identifier);

b) study title (abbreviated name, where applicable);

c) study type (e. g., randomised clinical trial, cohort study, a case-control study);

d) the population under study, including the state and other characteristics of the population (e. g., pediatric population or patients with renal impairment);

e) study status: in progress (study started and ongoing) or completed (clinical study report completed).

Subsection 7.1. Completed Clinical Trials

624. This subsection should summarize the clinically important efficacy and safety data from clinical trials completed during the reporting period. This information shall be presented in a condensed form or the form of a synopsis. This subsection may also include information that confirms or disproves previously identified safety signals and contain evidence of newly detected safety signals.

Subsection 7.2. Ongoing Clinical Trials

625. Where the MA holder becomes aware of any clinically important information obtained in ongoing clinical trials (e. g., identified during an interim safety analysis or as a result of the unblinding of identified serious adverse events), it shall be summarised in this section. This subsection may also include information that confirms or disproves previously validated safety signals and evidence of new safety signals.

Subsection 7.3. Long-Term Follow-Up Monitoring of Patients' Conditions

626. Where any data are available on long-term follow-up monitoring of patients included in clinical trials, this subsection provides information on the results of such monitoring of data having significance for the safety profile.

Subsection 7.4. Other Therapeutic Use of the Medicinal Product

627. This subsection shall include clinically important safety information from other marketing authorisation programs using specific protocols that systematically collect safety data (e. g., accessibility programs, compassionate use program, individual access program, etc.).

Subsection 7.5. New Safety Data on the Fixed Combination Medicinal Product in Use

628. Unless otherwise specified by the authorised authorities of the Member States, the following data shall be provided for combination therapy:

a) where a medicinal product is approved for use as a component of fixed therapy or a multicomponent therapy regimen, the subsection shall summarize important safety data of the combination treatment;

b) where the medicinal product is a combination product, this subsection should summarize important safety information for each of the individual components.

Section 8. Data from Non-Interventional Studies

629. This section summarizes safety information or data derived from non-interventional clinical trials (e. g., observational studies, epidemiological studies, patient registries, active monitoring programs) organised by a MA holder that became available during the reporting period and affect the risk–benefit ratio assessment of a medicinal product. The section should include data related to aspects of the safety profile and obtained from the results of studies evaluating medicinal product use.

630. The MA holder must include in an annex to the periodic safety update report a list of all non-interventional studies organised by the MA holder and carried out to identify, characterize and quantify the safety profile aspects of concern, confirm the safety profile of the medicinal product or evaluate the effectiveness of risk minimisation measures that were performed or are being carried out during the reporting period (e. g., post-authorisation safety studies) with an indication of information on each of the studies in accordance with paragraph 623 of these Rules.

631. Final reports prepared during the reporting period shall be included in an annex to the periodic safety update report.

632. This section may include summarised information on the assessment of data obtained from the implementation of patient support programs if it is not included in other sections of the periodic safety update report. The description and assessment of signals or risks identified by the MA holder during the execution of these programs are included in Section 16 of the periodic safety update report.

Section 9. Data from Other Clinical Trials and Data Obtained from Other Sources

Subsection 9.1. Data from Other Clinical Trials

633. The subsection must summarize information related to the risk–benefit ratio assessment of a medicinal product and be obtained from the results of other clinical trials to which a MA holder had access in the reporting period (for example, the results of meta-analyses of randomised clinical trials, safety data from the development partners of a medicinal product, etc.).

Subsection 9.2. Medication Errors

634. The subsection shall summarize information that reflects the data obtained during the reporting period on cases of medication errors or potential medication errors, including those not accompanied by the development of adverse reactions. A medication error can occur at any stage of the drug administration process and can be associated with a patient, consumer, or healthcare professional. A potential medication error may or may not be patient-related and is a case in which circumstances are generated, leading to application error. According to a MA holder’s assessment, the section provides information that can be considered when interpreting safety data or assessing the risk–benefit ratio of a medicinal product.

Section 10. Data from Preclinical (Non-Clinical) Studies

635. This section summarizes information relevant to the safety profile from *in vivo* and *in vitro* preclinical (non-clinical) studies (e. g., carcinogenicity, reproductive toxicity, or immunotoxicity studies) performed or completed during the reporting period. The results of studies that have been carried out to investigate certain safety concerns shall be presented in the section regardless of

the data obtained. An assessment of the obtained data impact on the safety profile shall be presented in the “Signals and Risk Assessment” section and the “Integrated Risk–Benefit Analysis for Approved Indications” section of the periodic safety update report.

Section 11. Scientific Medical Literature Data

636. The section presents a summary of new and relevant safety data published in the peer-reviewed scientific medical literature or were obtained from unpublished monographs relevant to a medicinal product and became available to a MA holder during the reporting period.

637. Searching for information in scientific medical literature to prepare a periodic safety update report shall be broader than a search for individual case safety reports in scientific medical literature. It should also include studies that have assessed safety outcomes of adverse reactions in study groups.

638. Special safety aspects that shall be considered when searching for information, but which may not be detected when performing searches to obtain data on individual cases of adverse reactions, include:

pregnancy outcomes (including termination of pregnancy) that were not accompanied by undesirable consequences;

use of a medicinal product in a pediatric population;

implementation of compassionate use programs and personalised prescription programs;

lack of efficacy of a medicinal product;

asymptomatic overdose;

inappropriate general characterisation of the medicinal product, and inappropriate use of the medication;

medication errors that were not accompanied by the development of adverse events;

important results of preclinical trials.

If applicable, this section shall also analyze information on other active ingredients of the pharmacological group to which the medicinal product belongs.

Section 12. Others Periodic Safety Update Reports

639. This section is created only in cases where, by agreement with the authorised authorities, a MA holder prepares more than one periodic safety update report for the medicinal product (in the case of a fixed combination medicinal product, a medicinal product with multiple indications and/or different dosage forms). As a rule, the MA holder shall prepare one periodic safety update report for one active ingredient (unless otherwise determined by the authorised authority). In special cases, by decision of the authorised authorities, the holder prepares a series of periodic safety update reports for one medicinal product. Simultaneously, in this section of each subsequent periodic safety update report of such a series, significant safety data from other periodic safety update reports shall be summarised, unless such a summary is presented in other sections of this report.

640. Where other marketing authorisation holders, sponsors of clinical trials or other partners have access to data from periodic safety update reports for similar medicinal products, the marketing authorisation holder shall provide a summary of the relevant safety data obtained from their periodic safety update reports for the reporting period.

Section 13. Insufficient Therapeutic Efficacy of the Medicinal Product Established in Controlled Clinical Trials

641. Should data obtained when performing clinical trials for medicinal products used for the treatment and prevention of serious and life-threatening

diseases indicate their insufficient therapeutic efficacy or insufficient therapeutic efficacy for the treatment being carried out, such data indicate the significant risk for the target population and shall be analysed and summarised in this section of the periodic safety update report.

Section 14. Important Information Received on Completion of the Periodic Safety Update Report Preparation

642. This section summarizes potentially important safety and efficacy data obtained after the data lock point but before the final version of the periodic safety update report. Such data include significant clinical data from new publications, significant data obtained from post-treatment follow-up of patients, clinically important toxicological data, and information about the actions taken by the MA holder, independent data assessment committees, and authorised authorities regarding the problems related to the medicinal product's safety profile. New individual case safety reports shall not be included in the section unless they represent a critical case of an adverse reaction (e. g., the first reported case of an important adverse event in a person), or contain an important safety signal or additional information to assess the safety concern reported in the periodic safety update report. The section also includes safety information identified during this period, which implies introducing significant changes in the reference information on the medicinal product (e. g., on a new adverse reaction, caution, or contraindication). Data from this section shall be taken into account when compiling Subsection 16.3 "Risk Assessment and New Information" of Section 16 "Signals and Risk Assessment" of the periodic safety update report

Section 15. Signal Review (New, Pending, and Completed)

643. The purpose of this section is to provide a review of the detected signals, signals received during the adverse reaction assessment period, and signals received during the reporting period, whose assessment has already been completed. This section shall include the signals for which the first stage of the assessment has been completed, and the feasibility of the subsequent assessment stages has been determined according to the validation results. Signals can be identified by a qualitative method (e. g., based on the receipt of one or a series of adverse reaction reports) or a quantitative method (e. g., based on a disparity score, clinical or epidemiological studies), and can also be the result of a request for providing safety information from the authorised authority (any country in the world).

644. The MA holder submits the decision on the subsequent classification of signals, as well as conclusions on the results of the assessment performed, including the medical assessment and scientific interpretation of the data available in Section 16 “Signal or Risk Assessment” of the periodic safety update report.

645. Newly identified signals include signals that were identified during the reporting period. Clinically important new information obtained during the reporting period regarding a previously closed signal shall also be considered a new signal based on identifying new aspects of a previously rejected signal or determining that further verification of existing data is required. New signals may be classified as closed or pending, depending on these signals’ status at the end of the reporting period of the periodic safety report. For example, new signals include the receipt of new information, which assessment results suggest that the following actions may be taken or required:

resuming work on a previously closed or rejected signal on the result of receiving new information;

a possible clinically important difference in the characteristics of the identified risk in terms of severity or frequency of occurrence has been determined (e. g., new information suggests the possibility of a more serious outcome in the form of liver failure on the previously described manifestation of transient elevation of liver enzyme activity or for previously described neutropenia, agranulocytosis has been reported with other alternative causes of this condition excluded);

possible differences in the identified risk characteristics in terms of its severity or frequency of occurrence for a particular patient subgroup were determined;

it is assumed that precautions or special indications, contraindications, changes in indications or target populations, or other risk minimisation measures will need to be added (where the potential risk is confirmed).

646. The MA holder shall provide in tabular form the following information on signals under consideration or closed as of the end of the reporting period (in this section of the report or in an annex thereto):

a brief description of the signal;

date of signal detection by the MA holder;

signal status as of the end of the reporting period (pending or completed);

signal closing date, where applicable;

a brief summary of key data;

plans for further signal assessment;

actions taken or planned.

647. A detailed description of closed signal assessment is not included in this section and shall be provided in Subsection 16.2 “Signal Assessment” of the periodic safety update report. Assessment of new information on previously

identified or potential risks, which has not been assessed as a new signal, is presented in Subsection 16.3 “Assessment of Risks and New Information” of the periodic safety update report.

648. Where the MA holder, at the authorised authority’s request, has assessed a particular issue arising from the medicinal product use and not classified as a signal, and the analysis results have not confirmed that the issue shall be classified as a signal, the section provides summarised information describing the assessment results obtained. If the assessment results indicate that the problem shall be classified as a signal, the information shall be included in Subsection 16.2 “Evaluation of Signals” (in the tabulate data on signals) of the periodic safety update report.

Section 16. Signals and Risk Assessment

649. The purpose of this section is to provide:

a summary of known and unknown characteristics of the important identified, important potential risks, and missing information as of the beginning of the reporting period in accordance with the periodic safety update report;

assessment of all signals closed for the reporting period;

assessment of new information on important previously identified and important potential risks;

summary of the effectiveness of risk minimisation measures.

This section’s information shall not duplicate the data presented in other sections of the periodic safety update report and shall reflect the interpretation and critical assessment of the available data to characterize the risks assessed as important for a medicinal product. It is usually not required to describe individual cases in the section providing summarised analytical information. Still, the description of the clinical assessment of individual cases can be

justified if these cases provide characterisation and clinical assessment of the risk manifestation.

Subsection 16.1 Summarised Information on Safety Concerns

650. The purpose of this subsection is to provide a basic summary of important safety concerns about the medicinal product, indicating, for each safety aspect, information about what new assessment of this aspect can be performed.

651. When determining the importance of each aspect of risk, the following factors should be considered:

a) severity of the drug-related risk from a medical point of view, including the effect on patients' condition;

b) frequency, predictability, preventability, and reversibility of risk;

c) potential impact on public health (health of the population) (frequency of risk in the population, size of the population exposed);

d) assessment of the public acceptability of the risk in cases of the medicinal product's possible impact on public health (health of the population) (e. g., refusal of the vaccination program).

652. The summarised information shall represent the available safety data for a medicinal product as of the beginning of the reporting period in accordance with the periodic safety update report and reflect:

a) important identified risks;

b) important potential risks;

c) missing information.

653. For medicinal products with a safety specification, the information included in this subsection shall be consistent with the summarised information provided in the current version of the safety specification at the

start of the reporting period in accordance with the periodic safety update report.

654. Concerning medicinal products that do not have a safety specification, this subsection should provide information about the important identified and potential risks and missing information related to the product use based on the pre-authorisation and post-authorisation period, including the following information:

about important adverse reactions;

about interactions with other medicinal products;

about medication errors detected;

about Interaction with food or other substances;

about the occupational exposure;

about class-specific pharmacological effects.

Summarised data on missing information shall assess the severity of gaps in available knowledge on particular aspects of safety profile for target populations.

Subsection 16.2. Signal Assessment

655. The information provided in this subsection shall summarize the results of the safety signal assessment that was completed during the reporting period. Signals can be closed based on the assessment conducted due to signal rejection or signal confirmation and attributed to the number of important potential or identified risks. The subsection includes an assessment for two categories of signals:

based on the assessment results, signals that can be classified as potential or identifiable risks, including the lack of therapeutic efficacy;

according to the assessment results, signals that were rejected as false signals based on a scientific assessment of the information available at the

procedure’s date. For each of the categories of signals, a detailed description shall be provided with a detailed rationale of the MA holder’s conclusions regarding signal rejection, or attribution to the number of potential or identified risks. The scope and level of detail of the submitted description of the signal assessment performed depend on the medical significance of the safety aspect (e. g., seriousness, reversibility, outcomes that increase morbidity and mortality), the potential impact on public health (e. g., the prevalence of use, frequency, and significance of use not in line with the summary of product characteristics), and the extent of the evidence base for the signal. Where the section includes assessment data on several signals by two categories, the information should be presented in the following order:

closed and false signals;

closed signals classified as important potential risks;

closed signals classified as important identified risks;

closed signals, defined as potential risks and not classified as important ones;

closed signals, defined as identified risks and not classified as important ones;

The assessment of closed signals shall be presented subject to indications or subject to populations, where applicable.

Signal assessment can include assessing preclinical and clinical data and should be exhaustive concerning possible sources of information.

As part of the signal management process, the signal assessment by the authorised authority after conducting the initial analysis and prioritisation of the signal implies assessing all available signal data to determine the need for regulatory action.

656. Signal description assessment shall be included in this subsection of the periodic safety update report or presented as an annex to the report and contain information on the following aspects:

a) source or driving moment of the signal formation;

b) assessment-related justification;

c) assessment methods, including data sources, search criteria (where applicable), MedDRA terms used to review (e. g., preferred level, top-level, system organ class, etc.) or standardised MedDRA queries) or analytical approaches;

d) critical analysis results (summarised information) of the data considered when assessing the signal. In cases where this is considered important, the results may include a description of a series of cases or an individual case of an adverse reaction);

e) discussion;

f) conclusion, including the actions proposed;

Subsection 16.3. Assessment of Risks and New Information

657. A MA holder shall submit a critical assessment of new information on previously identified risks for the reporting period, which has not been included in Subsection 16.2 “Signal Assessment” of the periodic safety update report. New safety information that constitutes a signal for a previously identified risk or a previously rejected signal shall be presented in a tabular format and included in Subsection 16.2 “Signal Assessment” if the signal has been closed during the reporting period of the periodic safety update report. This subsection provides updated information on previously identified risks, which is not assessed as a signal. Examples of this information are data that confirm a potential risk with a change in its

classification attribution to an identified risk or data obtained to supplement the characterisation of a previously identified risk.

658. New information shall be presented on the following risk aspects:

a) important potential risks;

b) important identified risks;

c) other potential risks not classified as important ones;

d) other identified risks not classified as important ones;

e) updated data on missing information.

659. The assessment shall focus on new information obtained during the reporting period and justified interpretation of the impact the obtained information produces on the risk understanding and characterisation. Based on the impact assessment performed, an update of the characteristics of important potential and important identified risks can be made in Subsection 16.4 Risk Characteristics of the periodic safety update report. The level of detail of the assessment’s description should be consistent with the available evidence base for these risks and the significance of their impact on public health (health of population).

660. A description of the assessment of new information carried out, or an update of missing information shall be included in this subsection of the periodic safety update report or presented as an annex to the report and include the following aspects:

the source or reason for signal generation;

justification related to the assessment;

assessment methods, including data sources, search criteria, or analytical approaches;

critical analysis results (summarised information) of the data considered when assessing the signal;

discussion;

conclusion, including a conclusion regarding confirmation or rejection of the grounds for updating the characteristics of important potential or identified risks, according to the assessment of new information for the reporting period.

The subsection shall reflect and critically assess all new information on the populations exposed to the medicinal product during the reporting period and provide data on missing information and unresolved problems. All aspects of data veracity shall be objectively indicated.

Subsection 16.4. Risk Characteristics

661. This subsection describes the important identified risks and important potential risks based on cumulative data (including those not limited to the reporting period) and describes the missing information.

662. Considering the source of the data, the risk information shall include the following data (where applicable):

frequency;

number of cases detected (numerator) and the estimate’s accuracy, considering the data source;

volume of prescriptions (denominator), expressed as the number of patients, patient-months (patient-years), etc., and the estimate’s accuracy;

assessment of the relative risk and its accuracy;

assessment of the absolute risk and its accuracy;

impact on the patient (symptoms, quality, and number of years of life);

impact on public health (health of population);

risk factors (e. g., individual risk factors (age, pregnancy, lactation period, impaired liver or kidney function, significant comorbidity, severity of diseases, genetic polymorphism, race, and/or ethnicity);

dose, route of administration;

duration of treatment, period of risk;

preventability (predictability is assessed, the ability to monitor the condition by indicator symptoms or laboratory parameters);

reversibility;

potential mode of action;

level of evidence and uncertainty, including analysis of conflicting facts (if any).

If the missing information is considered important, the relevant information is included in the list of safety concerns. Information shall be provided with the indication of the limitations of the available database (considering the number of patients included in the study, cumulative exposure or long-term use, and other restrictions).

663. When preparing a periodic safety update report for medicinal products with several indications, dosage forms, or modes of administration, if there are significant differences in identified and potential risks, it may be justified to present risk data separately by indication, dosage form, or route of administration. The report may contain the following information:

a) risks specific to the active ingredient;

b) risks specific to certain dosage forms or routes of administration (including occupational exposure);

c) risks specific to certain populations;

d) risks associated with medication use without a doctor’s prescription (for active ingredients that are available in prescription and over-the-counter forms).

Subsection 16.5. Effectiveness of Risk Minimisation Measures (where applicable)

664. Risk minimisation measures include actions to prevent adverse reactions arising from exposure to the medicinal product or to reduce the severity of their occurrence. Risk minimisation activities aim to reduce the likelihood or severity of adverse drug reactions. Risk minimisation measures include routine measures (e. g., changes in the general characteristics of the medicinal product) or additional measures (e. g., direct contact with healthcare professionals, preparation and distribution of educational materials).

665. The subsection shall present the results of assessing the effectiveness of risk minimisation measures. Relevant information on the effectiveness and/or limitations of specific risk minimisation measures in relation to important identified risks that was obtained during the reporting period is presented in a generalised form. The results of assessing the risk minimisation measures effectiveness obtained in one Member State, which can be useful and used in the other Member States, are important and shall be presented in the report. The results of assessing the risk minimisation measures effectiveness obtained during the reporting period in a particular region are presented in the regional annex to the report.

Section 17. Benefit Assessment

666. In this section, Subsections 17.1 “Important Core Efficacy Information on the Medicinal Product” and 17.2 “Newly Identified Efficacy Information” provide the main obtained and newly detected efficacy information on the medicinal product, which forms the character of the benefit of the medicinal product which is to be described in subsection 17.3

“Benefit Characteristics” with subsequent inclusion in Section 18 “Integrated Risk–Benefit Analysis for Approved Indications”.

Subsection 17.1. Important Core Efficacy Information on the Medicinal Product

667. This subsection provides the core information on the medicinal product’s efficacy in clinical trials and when used in medical practice (as of the beginning of the reporting period). This information shall be relevant to the approved indications for use in the medicinal product’s reference information.

668. For medicinal products with multiple indications, target populations, and/or routes of administration, the benefits shall be characterised separately for each factor.

669. For medicinal products in which significant safety or efficacy changes were detected during the reporting period, this subsection should include sufficient information to justify the medicinal product’s updated benefit characteristics, as reflected in Subsection 17.3 “Benefit Characteristics” of the periodic safety update report. The content and level of detail of the information provided in this section shall be sufficient to justify the benefit characteristics in subsection 17.3 “Benefit Characteristics” and the assessment of the risk–benefit ratio in Subsection 18 “Integrated Risk–Benefit Analysis for Approved Indications” and may include (where necessary) the following aspects:

a) epidemiology and origin of disease;

b) benefit characteristics (e. g., diagnostic, preventive, symptomatic, disease-modifying);

c) important endpoints supporting benefit (e. g., effects on mortality, symptomatology, outcomes);

d) evidence of efficacy in clinical trials and medical practice compared with a comparator (e. g., comparative controlled clinical trials, meta-analyses, observational studies);

e) trends and/or evidence of benefit for important population subgroups (e. g., age, gender, ethnicity, disease severity, genetic polymorphism) if relevant to risk–benefit assessment.

Subsection 17.2 Newly Identified Efficacy Information

670. For medicinal products during the reporting period, new information on efficacy may be obtained in clinical trials and medical practice, which shall be presented in this subsection. New information on efficacy in real medical practice (if any) may be provided concerning the approved indications. Information on the evidence base for disapproved indications is not included in the section in case it is relevant to the risk–benefit ratio assessment.

671. When used for new indications approved during the reporting period, efficacy information on the medicinal product shall also be reflected in this subsection. The content and level of detail of the information provided in the subsection shall be sufficient to justify the benefit characteristics in subsection 17.3 “Benefit Characteristics” and to assess the risk–benefit ratio in subsection 18, “Integrated Assessment of the Risk–Benefit Ratio of the Medicinal Product” of the periodic safety update report.

672. This subsection focuses on vaccines, antimicrobial and other medicinal products for which changes in the therapeutic environment may affect the risk–benefit ratio over time.

Subsection 17.3. Benefit Characteristics

673. This subsection provides a consolidated baseline and emerging therapeutic benefit data that became known during the reporting period (for approved indications).

674. If there are no new data on the efficacy profile and no significant changes in the safety profile, this subsection should contain a reference to Subsection 17.1 “Important Core Efficacy Information on the Medicinal Product Obtained During Clinical Trials and Use in Medical Practice” of the periodic safety update report.

675. If new information on the therapeutic benefit was received during the reporting period and there were no significant safety changes, the section summarizes the combined data on the baseline and new information.

676. If there are significant changes in the safety profile or new data are obtained that suggest a significantly lower level of therapeutic benefit than initially demonstrated, this subsection shall provide a brief critical assessment of the evidence base for safety and efficacy in clinical trials and medical practice, indicating the following information:

a) a summary of the evidence-based data on therapeutic benefits (an assessment is made of the comparative aspect of efficacy, the severity of the effect, the correctness of statistical processing, the weak and strong aspects of the methodology, the consistency of data in different studies);

b) new information that questioned surrogate endpoints (if any);

c) clinical significance of the severity of the therapeutic effect;

d) the possibility of generalizing information about the therapeutic effect in the target subgroups (e. g., information about the lack of a therapeutic effect in any population subgroup);

e) adequacy of the dose–therapeutic response relationship;

f) effect duration;

g) comparative efficacy;

h) determination of the extent to which efficacy data obtained from clinical trials can be summarised subject to the populations for which the medicinal product is used in medical practice.

Section 18. Integrated Risk-Benefit Ratio Analysis for Approved Indications

677. In the section, the MA holder shall provide a summarised assessment of the medicinal product's benefits and risks when used in clinical practice. The critical analysis and consolidated information are provided based on the previous sections' data in terms of benefits and risks without duplicating the information contained in Subsection 16.3 "Assessment of Risks and New Information" and Subsection 16.4 "Benefit Characteristics" of the periodic safety update report.

Subsection 18.1. Integrated Analysis in the Context of the Risk–Benefit Ratio (Including the Medical Need and Important Alternatives)

678. This subsection provides a summary of the medical need for a medicinal product based on the approved indication summarised subject to alternatives or alternative treatment (medical, surgical or other methods, including no treatment).

Subsection 18.2 Assessment of the Procedure for Analyzing the Risk–Benefit Ratio

679. The risk–benefit ratio has different values depending on the indication and target populations. Therefore, for medicinal products authorised for several indications, the risk–benefit ratio shall be assessed

separately for each indication. If there are significant differences in the risk–benefit ratio between subgroups within one indication, an assessment of the risk–benefit ratio shall be presented separately and for population subgroups (if possible).

680. The subsection shall provide basic information on risk and benefit assessment:

a) the key risk and benefit information from in the preceding sections combined to assess their balance;

b) assessment of the context of the medicinal product use (cure, prevention, diagnosis), the disease severity and seriousness, the target population (relatively healthy, with chronic diseases, rare conditions);

c) as for the benefit, its nature, clinical significance, duration and severity of effect, the possibility of distributing the obtained data to the entire population, evidence of efficacy in patients who do not respond to alternative treatment, individual aspects of benefit are assessed.

d) as for the risk, clinical significance (e. g., the nature of toxicity, severity, frequency, predictability, preventability, reversibility, impact on the patient), including risk aspects associated with the medicinal product use not in accordance with the indications included in the approved summary of product characteristics, use based on unapproved indications or in unapproved populations in clinical trials, and misuse are assessed;

e) when formulating the of the “benefit-risk” ratio assessment, strong and weak points, as well as the uncertainty of the evidence base in terms of the risks and benefits, describing their impact on the assessment (specifying the characteristics of the assessment limitations).

681. To assess the risk–benefit ratio, a description and reasoning of the methodology used along with the following information are provided:

assumptions which confirm the conclusion made on the risk–benefit ratio assessment;

comments on the possibility of expressing risks and benefits in the form used for presentation and the possibility of their comparison;

in the case of a formal quantitative or semi-quantitative assessment of the ratio, a summarised description of the assessment methods is included.

Economic assessment (e. g., cost–efficacy) shall not be considered when assessing the risk–benefit ratio.

In case of receiving new important information or preparing a periodic safety update report at the authorised authority's request, the MA holder must carry out a detailed assessment of the risk–benefit ratio based on cumulative data on benefits and risks. Where little new information has been received during the reporting period, the risk–benefit ratio assessment shall be aimed at evaluating the updated safety data obtained during the reporting period.

Section 19. Conclusion of the Periodic Safety Update Report and Suggested Follow-Up Actions

682. The final section of the periodic safety update report shall contain an opinion on the impact of new information identified during the reporting period on the overall assessment of the risk–benefit ratio for each approved indication, as well as by patient subgroup (if applicable).

683. Based on the assessment of cumulative safety data and the risk–benefit ratio analysis, a MA holder shall assess the need to change the reference information for a medicinal product and propose the appropriate changes.

684. If necessary, the conclusion shall include preliminary proposals for optimisation or further assessment of the risk–benefit ratio, including risk

minimisation measures, with a view to their subsequent discussion with the Member States' authorised authorities.

685. As regards medicinal products that have a plan for pharmacovigilance and risk minimisation, change proposals, where necessary, shall be included in the plan.

686. Based on the assessment of cumulative safety data and an assessment of the risk–benefit ratio, the MA holder shall conclude the periodic safety update report regarding the need to make changes to the reference information for the medicinal product and/or perform additional pharmacovigilance activities or risk minimisation. Proposed changes to the reference information on the medicinal product use (summary of product characteristics and package inserts) shall be described in this section.

Section 20. Annexes to a Periodic Safety Update Report

687. This section shall include annexes containing the following information:

a) reference information;

b) summarised tabular data on serious adverse events identified during clinical trials and interval summarised tabular data on serious and non-serious adverse reactions separately based on post-authorisation data;

c) tabular data on signals (if not included in the main part of the periodic safety update report);

d) a list of all post-authorisation interventional and non-interventional safety studies sponsored by the MA holder that are aimed to identify, characterize and quantify safety concerns, confirm the safety profile of the medicinal product, or assess the effectiveness of risk minimisation measures;

e) A list of information sources that were used to prepare the periodic safety update report.

f) Proposed projects of information on a medicinal product (summary of product characteristics and package inserts).

g) information on proposed additional pharmacovigilance activities and risk minimisation measures (the annex shall include information on the MA holder's planned submission of a risk management plan or the risk management plan update);

h) Summarised information on safety concerns about the medicinal product following the version of Module CVII of Section II of the risk management plan as of the beginning of the reporting period.

i) data of final reports of post-authorisation interventional and non-interventional safety studies sponsored by the MA holder, the purpose of which is to identify, characterize and quantify safety concerns, confirm the medicinal product's safety profile, or assess the effectiveness of risk minimisation measures;

j) data of reports on the results of studies or other activities to assess the effectiveness of risk minimisation measures.

7. Quality System for the Periodic Safety Update Report at the MA Holder Level

688. As part of the MA holder's quality system, structures and processes shall be developed for the preparation, quality control, review and submission of a periodic safety update report, including monitoring the procedure performance during and after their assessment. They shall be described as procedures and executed in the form of written documents.

689. Pharmacovigilance processes include several areas that can have a direct impact on the quality of the periodic safety update report (e. g., the processing of reports of adverse reactions received as part of spontaneous reporting or clinical trials, scientific and medical literature review, detection,

validation, and assessment of the signal, additional measures on pharmacovigilance and post-authorisation study activities, procedures for processing and combining data in assessing benefits and risks, etc.). The quality system shall describe the relationship between processes, information channels, and responsibilities for procedures to collect the information for inclusion in the periodic safety update report. Documented procedures for controlling the quality of the processes shall be developed and implemented to ensure the data's completeness and accuracy in the periodic safety update report. Based on the importance of an integrated risk–benefit assessment, it should be ensured that various departments contribute to preparing the periodic safety update report.

690. The periodic safety update report should contain an assessment of special safety-related requests from the Member States' authorised authorities. The MA holder shall develop and implement a mechanism to ensure that such requests are properly handled and responded to.

691. The summarised tabular data shall be verified in terms of the MA holder's databases in order to ensure the accuracy and completeness of the reported data on adverse reactions and events. The processes for placing queries in the database, the parameters used to retrieve the data, and quality control shall be properly documented.

692. The MA holder's quality system shall exclude any risk of the registrant's failure to comply with legal requirements and the following risks:

failure to submit a report, including complete failure to submit a periodic safety update report, violation of the schedule or deadlines for submitting the said report (without prior agreement with the Member States' authorised authorities);

unreasonable failure to provide the requested information;

poor reporting quality (poor documentation or insufficient information or assessment submitted to analyze new safety information, safety alerts, risk assessments, benefit assessments and integrated risk–benefit analysis, no indication of misuse, no standard terminology, unjustified exclusion of cases, failure to provide information on risk factors);

submission of a periodic safety update report without reflecting previously received requests from the Member States' authorised authorities.

693. All significant deviations from the procedure for preparing and submitting a periodic safety update report shall be documented, and appropriate corrective and preventive actions shall be taken for their correction. This documentation shall be available at all times.

694. In the case of delegation of responsibilities for preparing a periodic safety update report to third persons, the MA holder must ensure that the third person has an adequate quality system that meets the requirements of the Union's legal acts and the Member States' legislation.

8. Training of Personnel on Procedures for Periodic Safety Update Report

695. The authorised pharmacovigilance officer is responsible for ensuring that pharmacovigilance, health information assessment, and quality control personnel involved in the preparation, review, quality control, evaluation, and submission of a periodic safety update report is properly experienced, qualified, and trained. Training in various knowledge and skills in the pharmacovigilance area should be provided. The areas of training shall include familiarisation with the rules of the Union law and the Member States' legislation, guidelines, scientific assessment of data, procedures for preparing a periodic safety update report. Training completion shall be documented prior to performing the functions of preparing the periodic safety update report.

9. Procedure for Submitting a Periodic Safety Update Report

Standard Procedure for Submitting a Periodic Safety Update Report

696. The frequency and timing of submission of a periodic safety update report on medicinal products are determined following the list approved by the Member States' authorised authorities.

697. For medicinal products, the international non-proprietary name or group name of which is not included in the specified list, the frequency of submission of a periodic safety update report is:

every 6 months from the international birth date for the first 2 years;

annually for the next 2 years;

thereafter, every 3 years.

The deadline for submitting a periodic safety update report is no more than 90 calendar days from the data lock point.

The Procedure for Submitting a Periodic Safety Update Report for Generics, Well-Established Use Products, Herbal Medicinal Products, Homeopathic Products Authorised or Aligned with the Right of the Union.

698. A periodic safety update report for generics, well-established use products, herbal medicinal products, homeopathic products authorised in the Member States or aligned with the right of the Union shall not be submitted, except for the following cases:

obligation to submit a periodic safety update report is established upon the product authorisation by the reference state's authorised authority (expert organisation);

obligation to submit a periodic safety update report is established based on the pharmacovigilance system's identified data;

absence of an approved original medicinal product for generics in a Member State territory.

699. The Member States' authorised authority has the right to request the submission of a periodic safety update report from a holder of the MA for a generic medicinal product, a medicinal product with well-studied medical use, herbal medicinal product, a homeopathic medicinal product.

700. Holders of marketing authorisations for medicinal products, who are not required to regularly submit a periodic safety update report, shall ensure that all procedures and measures stipulated by these Rules are carried out to ensure continuous safety monitoring throughout the medicinal product's life cycle and immediately submit to the authorised authority all information that may influence on assessing the risk–benefit ratio of a medicinal product.

Extraordinary Submitting of a Periodic Safety Update Report

701. A periodic safety update report shall be submitted immediately. The preparation of a periodic safety update report shall be carried out within no more than 60 calendar days from the date of receipt of a written request from the Member State's authorised authority.

10. Form for Submitting a Periodic Safety Update Report

702. A periodic safety update report shall be submitted in electronic form with the possibility of text search in Russian or English with the obligatory translation into Russian of the following sections: a summary of the main content, an integrated analysis of the risk–benefit ratio according to approved indications, and conclusion. At the request of the Member State's authorised authority, a MA holder is obliged, within 30 calendar days from

the date of receipt of such a request, to submit a translation into Russian of other sections of the periodic safety update report.

11. Assessment Process for a Periodic Safety Update Report in the Member States Territories

703. The Member States' authorised authorities shall ensure that the periodic safety update report is assessed to determine the report's compliance with the requirements of the Union law and the Member States' legislation and detect possible changes in the safety profile of a medicinal product and the impact of these changes on the assessment of the risk–benefit ratio of a medicinal product.

IX. Signal Management

1. Signal Sources and Their Processing

704. Signal sources include all data from drug use, including preclinical and clinical data, pharmacovigilance data, and quality control systems. Data may include information obtained by spontaneous reporting systems, active monitoring systems resulting from non-interventional studies, clinical trials, and other sources.

705. The most common signal sources are spontaneous adverse reaction reports, active forms of drug safety monitoring, clinical trials, articles in the scientific medical literature.

706. In many cases, signal detection results from ongoing periodic monitoring of adverse reaction databases, including the adverse reaction databases of MA holders, authorised authorities, databases of the World Health Organisation. Signals can be detected in various studies, including preclinical, interventional, and non-interventional studies, systematic

reviews, and meta-analyses. Various types of active monitoring can help detect signals and stimulate the process of reporting certain types of adverse reactions by specialists.

707. Other sources of information include Internet sources (public websites, social networks, blogs) or other sources through which patients and consumers can report experiences of adverse drug reactions.

2. Signal Detection Methodology

708. Signals shall be detected in accordance with a structured and recognised methodology that considers the characteristics of the data (e. g., time on the market, exposure to patients, target population) and may vary depending on the type of medicinal product for which the procedure is being performed. For example, specific methodologies may apply to vaccines and other biological medicinal products. Data obtained from all monitored sources of information shall be taken into account while detecting signals.

709. To assess the evidence base confirming the received signal, it is necessary to apply a structured and recognised methodology, which shall take into account clinical significance, the degree of reliability of the relationship between the medicinal product and the adverse reaction, the consistency of the data on the new relationship (or aspect of the relationship), the relationship between the degree of exposure and response, causal link between the medicinal product and the adverse reaction, biological plausibility, experimental results, data similar in nature to the adverse event.

3. Signal Processing

General Provisions

710. Signal processing includes the stages from signal detection to making recommendations. Signal processing rules apply to all stakeholders involved in the safety control of authorised medicinal products.

711. Signal processing includes the following stages:

a) signal detection;

b) signal validation;

c) signal prioritisation;

d) signal assessment;

e) recommendations for action;

f) exchange of information.

712. Working with the individual available information sources used to detect signals may require flexibility in signal processing, in particular:

where signal detection is based on a review of individual case safety reports, the signal detection procedure may include verification and prior prioritisation of the detected signal;

where a signal is detected based on the pooled survey results, it is generally not possible to assess each individual report, and additional data collection may be required as a result of validation.

Procedure (followed by a decision in accordance with the legal acts of the Union authorities and the Member States' legislation) and the exchange of information are components that need to be considered at each stage of the process.

Signal Detection

713. The following requirements apply to all signal detection methods:

a) the method used shall be appropriate for the data size (e. g., the use of complex statistical methods may not be suitable for small data);

b) it is necessary to consider data from all relevant sources;

c) systems must be implemented to guarantee the quality of the data detection activities performed;

d) a qualified person shall evaluate the cumulative data review results in a timely and appropriate manner;

e) upon detection of a threat to public health (health of the population), immediate and effective action shall be taken;

e) process for identifying signals should be adequately documented, including a rationale for the method and frequency of actions to be taken to detect signals.

714. The detection of safety signals can be based on an overview of databases of individual case safety reports, statistical analysis of large databases, or a combined approach based on a combination of these methods.

Review of Individual Case Safety Reports

715. Individual case safety reports may come from spontaneous reporting, as a result of active forms of monitoring, clinical trials, or published in the scientific medical literature. The presence of one report of a serious or severe adverse reaction (e. g., anaphylactic shock) may be sufficient to take further action. The information to be assessed shall include information on the number of reports (after excluding duplicate reports and reports that are misrepresented), patient demographics (such as age and gender), data on the suspected medicinal product (such as the dose administered) and an adverse reaction (such as signs and symptoms), temporal relationship between use of the drug and the development of an adverse reaction, clinical outcome due to continued or discontinued use of the medicinal product, the presence of potentially alternative causes for the development of an adverse event, the reporter’s assessment of the causal link,

and the information on reliability of the biological and pharmacological relationship.

Statistical Analysis of Large Databases

716. There are various statistical methods for automatically detecting signals based on the disproportionate number of reports, i. e., a higher level of reporting of a suspected adverse reaction to the corresponding active ingredient or medicinal product than other active ingredients or products in the database. The statistical methods cannot be used in all situations. When using statistical methods and selecting criteria for signal detection, the amount of data, the completeness of available information, and the seriousness of the adverse reaction should be considered.

717. The frequency of statistical analysis of the database and the formation of a statistical report depends on the characteristics of the active ingredient or medicinal product, indications, and potential or identified risks.

Combination of Statistical Methods and Review of Individual Case Safety Reports

718. Statistical reports may be designed to detect suspected adverse reactions that meet predetermined criteria for adverse reaction frequency, adverse reaction severity, adverse reaction clinical significance, novelty, or statistical relationship between the development of an adverse reaction and medicinal product use. Such filtering methods can facilitate selecting the most important individual case safety reports considered in the first procedure stage. The indicator limit used in this filtering process (e. g., at least 3 reports) may vary depending on the suspected adverse reaction and signal’s clinical significance, the impact on public health (health of the population), and the medicinal product use prevalence.

719. When automatic screening is used in signal detection, the respective individual case safety reports should be further examined separately.

Regardless of the statistical method used, the signal detection procedure shall always include a clinical assessment. The statistical method is an additional method for signal detection and validation.

Signal Validation

720. When a signal is detected, the data is assessed to verify and confirm that the available information provides sufficient evidence to identify a new potential causal link between the medicinal product use and the development of an adverse reaction or a new aspect of a previously established relationship. The validation results determine the need for further signal assessment.

721. When performing the signal validation procedure, regardless of the source of its receipt, it is necessary to take into account:

a) prior signal information:

the extent to which information on adverse reactions is reflected in the medicinal product’s information (summary of product characteristics and package inserts);

reflection of a signal associated with an adverse reaction in information on other medicinal products with a similar active ingredient (different dosage form or other differences) to assess the possible dependence of the signal on the characteristics of a certain medicinal product and/or a certain dosage form of a product;

the signal has already been assessed in a periodic safety update or risk management plan, as part of a different regulatory process, or discussed at the scientific expert committee level.

As a rule, signals that are not related to those specified in this subclause are subject to validation. However, already known signals may require validation if there is a potential difference in the incidence, duration of persistence, severity, or outcome (e. g., a fatality) compared with data or characteristics included in the summary of product characteristics or previously reviewed by the Member State's authorised authority;

b) the level of formation of the evidence base to confirm the correlation, for example:

a total number of reports (after excluding duplicate cases), highlighting the number of reports confirming the existence of a relationship (e. g., cases with a reasonable temporal link, with positive results of cancellation and re-prescription of a medicinal product, excluding an alternative explanation or other causal factors), including a healthcare professional's assessment of relationship (at least as a possible relationship) with supporting observable deviations from relevant studies;

number of reports concerning the volume of patient exposure;

additional reported cases of conditions related to administration of the medicinal product (e. g., other MedDRA terms for clinical complications or varying degrees of severity of an adverse reaction);

consistency between cases in the evidence base (e. g., consistency in time before adverse reaction, repeated observations of adverse reaction symptoms);

data quality and documentation;

compliance with the internationally agreed case definition, if applicable (e. g., compliance with certain criteria for severe skin reaction (RegiSCAR scale), compliance with the accepted definition of adverse events after immunisation);

presence of a relationship between the dose and the manifestation of an adverse reaction;

presence of a possible development mechanism based on the biological or pharmacological probability of its implementation;

determination of disparity in reporting (where applicable);

clinical significance and context:

seriousness and severity of the adverse reaction;

outcome and reversibility of the adverse reaction;

new aspects of a known adverse reaction (e. g., severity, duration of persistence, outcome, frequency, or management);

development of an adverse reaction as a result of drug interactions;

development of an adverse reaction in a vulnerable patient group (e. g., in women during pregnancy, children, elderly patients, patients with risk factors);

development of an adverse reaction with a different application method (e. g., in case of overdose, dependence, improper use, use not following the summary of product characteristics or package inserts, medication error, use of an adulterated medicinal product).

722. Additional sources of information about signals may contain data that will complement the evidence base in terms of confirming or rejecting the assumption of a new relationship between an adverse reaction and a medicinal product, or a new aspect of such a known relationship; in this regard, they can be used when performing the subsequent signal assessment procedure, depending on the significance and availability of this information. These sources of information about the signal include:

clinical study data;

information on the development of such cases published in the scientific medical literature, including information on other active ingredients of a similar pharmacotherapeutic class of medicinal products;

information on the epidemiology of adverse reactions or comorbidities;

experimental and/or non-clinical data;

large adverse reaction databases in case of detection of a signal according to the databases of the authorised authority or MA holder;

healthcare databases, which can be used to obtain information on patients' characteristics or the characteristics of the medicinal product use;

information from regulatory authorities in other countries of the world.

723. A signal becomes validated if the verification process of all relevant documentation indicates a presumably new causal link or a new aspect of a known relationship between an adverse reaction and the medicinal product and, therefore, justifies further assessment.

724. A signal for which a presumably new causal link or a new aspect of a known relationship has not been confirmed during the validation process may require further analysis (e. g., in cases where there is insufficient documentation of the relevant case of adverse reaction). In such cases, new adverse reaction reports or follow-up results on previously reported cases from the post-authorisation follow-up period shall be repeatedly considered at appropriate time intervals to ensure that all relevant reports are recorded and reviewed.

725. When processing a signal at the organisational level, several peer-review stages and discussions may be required involving decision-makers of different levels. Based on the results of the validation, various decisions can be made, including confirmation or rejection of the signal validation (invalid signal), decision on the necessity to perform an additional assessment of the available data, assign the validated signal to a new risk or an unknown aspect

of a known risk with a proposal for subsequent actions (such as making changes to the background information and/or introducing risk minimisation measures), or rejecting the assumption of assigning the validated signal to a new risk or an unknown aspect of a known risk (rejected signal).

726. An unvalidated signal is recognised at this stage as a signal for which, based on the results of validation and assessment of the supporting data, it is determined that the available data are insufficient to suggest the presence of a new potential causal link or a new aspect of a known association and, accordingly, further signal analysis is not reasonable.

727. MA holders and the Member States's authorised authorities shall have tracking systems to record the results of signal validation, including examining and tracking the reasons why signals were not accepted as indicative of a presumably new causal link or a new aspect of a known relationship between an adverse reaction and the medicinal product, and information that would assist in finding such cases and evaluating signals.

Signal Prioritisation

728. A key element of the signal management process is the immediate determination of their impact on public health (health of the population) or the risk–benefit ratio of the medicinal product in exposed patients. When assessing this impact, the following factors are considered:

a) the severity, seriousness, outcome, reversibility of the adverse reaction and the possibility of its prevention;

b) assessment of patient exposure and frequency of adverse reactions;

c) the use of a medicinal product in vulnerable population risk groups and/or in population groups exposed to a different way of using a medicinal product (e. g., misuse or use not following the stated indications);

d) consequences of discontinuation of treatment concerning the development of the disease and the availability of therapeutic alternatives;

e) expected degree of influence of the planned regulatory measures (e. g., the addition of sections of adverse reactions, precautions, contraindications, the introduction of additional risk minimisation measures, stopping medical use, withdrawal from the market);

f) possible signal extension to other active ingredients of the similar pharmacotherapeutic class.

729. In certain circumstances, special attention shall be paid to signals that are discussed in the media or have a high level of significance for public health (health of population) (e. g., adverse reactions resulting from immunisation of the population) to immediately communicate the results of such an assessment to the public and healthcare professionals.

730. The result of the signal prioritisation procedure shall include a recommendation on the time frame for implementing subsequent stages in signal management. At each stage of working with a signal, if the information is available that determines the need to prevent or minimize risk, appropriate measures shall be taken promptly, including until the full scope of work on signal assessment is completed. All signal handling stages shall include clinical assessment and controls to quickly consider the information received and determine appropriate follow-up changes.

731. The result of the signal prioritisation procedure shall be entered into the tracking system with a justification for the assigned signal prioritisation level.

Signal Assessment

732. The purpose of the signal assessment is to examine further evidence of a causal link between a new risk and an active ingredient or

medicinal product, or study a change in a characteristic of a known risk, and subsequently determine whether additional data collection or regulatory action is needed. The assessment consists of a thorough pharmacological, medical, and epidemiological examination of the relevant signal's available information. The review should include available pharmacological, preclinical, and clinical data. It should be as complete as possible concerning information sources, including data from the marketing authorisation application of the medicinal product when applying for authorisation and subsequent changes, articles in scientific medical literature, spontaneous reports, and unpublished information from MA holders and the Member States' authorised authorities. It is also necessary to take into account the recommendations of external experts. If information is obtained from multiple sources, the level of evidence and restrictions should be considered to assess their contribution to the safety concern assessment. Cumulative information from different sources also requires the selection of internationally recognised terminology. In the absence of a terminological definition, it is required to use an operational definition.

733. In some cases, signals need to be assessed according to the therapeutic level or system and organ class or at the standardised query level (using terms from the MedDRA dictionary). Searching for information may require that the other medicinal products of the same class and other adverse reactions are included in search, for example, concerning other terms related to a complex disease (e. g., optic neuritis as a possible first sign of multiple sclerosis), an early stage of the reaction (e. g., prolongation of the QT interval) or clinical complications of a related adverse reaction (e. g., dehydration or acute renal failure).

734. Collecting information from different sources can take time. To optimize the process, a step-by-step signal assessment method can be used.

For a new signal of a severe adverse reaction, interim measures can be taken if the first phase of the assessment concludes, based on available information, that there is a potential risk that needs to be prevented.

4. Actions of the Member States' Authorised Authorities Following the Results of Signal Assessment

735. Actions of the Member States' authorised authorities following the results of signal assessment may vary according to the requirements established by the legal acts of the Union authorities or the Member States' legislation and the conclusions based on the results of the signal assessment.

736. Although recommendations are made after the signal has been assessed based on cumulative information, the need for action is assessed throughout the signal management process, determining the rationale and feasibility of earlier actions to minimize risk.

737. Actions based on the signal assessment results may include additional risk assessment or risk minimisation measures if the mechanisms for the development of the suspected adverse reaction indicate the possibility of preventing or reducing the severity of the adverse reaction. If the conclusion is based on limited information, a post-authorisation safety study may be required to investigate a potential safety concern or problem.

738. If the Member State's authorised authority sends a request to a MA holder to take additional actions, such a request shall indicate the time frame for completing the actions, including reports on achieved goals and intermediate results in proportion to the severity and impact of the safety concern on public health (health of population). The MA holder and the Member States' authorised authorities shall consider the possibility of conducting the study on time, taking into account the parameters of the safety concern under study, for example, the frequency of development and the need

for a prospective study design. Consideration should be given to temporary measures to ensure the safe and effective use of a medicinal product or eliminate the risk, including the possibility of temporary suspension of the medicinal product's marketing authorisation.

739. If there is no risk to patients, the Member State's authorised authority may decide that no further assessment or further action is necessary.

5. Exchange of Information

740. Exchange of information should be ensured between the Member States' authorised authorities, MA holders, and other participants to distribute information about signals, collect additional data, further assess the safety concern and make decisions on patient health protection.

741. The MA holders transmit relevant information about signals to the Member States' authorised authorities (which is part of the obligations for pharmacovigilance and monitoring the risk–benefit ratio of the medicinal product). Validated signals that may have an impact on public health (health of population) and the benefit-risk ratio of the medicinal product shall be transferred to the Member States' authorised authorities in accordance with paragraphs 756–757 of these Rules. Proposals for possible actions shall also be submitted where appropriate.

742. Authorised authorities of the Member States transmit the signal assessment results to MA holders.

6. Additional Requirements for Managing the Signal of Biological Medicinal Products

743. Like other medicinal products, holders of marketing authorisation for biological medicinal products shall ensure continuous monitoring throughout the life cycle to identify and assess potential new risks associated

with the safety or efficacy profile. Specific requirements are related to the inherent variability of the manufacturing process of biological medicinal products, potentially impacting the safety and efficacy profile, including the characteristics and clinical consequences of the risk of immunogenicity. On this basis, all signal management stages shall be performed for the MA holder's biological product and concerning the active ingredient. If a signal is detected, all necessary actions shall be taken to determine the cause, including identifying the suspected batch. The procedures performed shall be characterised by the required level of sensitivity to identify important and serious risks associated with changes in the manufacturing process or quality of the biological medicinal product and important inter-batch differences. For biosimilar medicinal products, procedures for identifying possible important differences from the reference biological medicinal product shall be performed throughout the entire life cycle. Besides, the clinically relevant consequences of potential immunogenicity risk (as theoretically defined for a biological medicinal product) shall be considered and monitored throughout the life cycle.

744. MA holders of biological medicinal products shall ensure that all possible measures, including the use of various methods and information sources, are carried out to obtain updated and reliable data regarding the specific biological product's actual use. The process of analyzing data on actual use and detected suspected adverse reactions shall be organised in such a way as to ensure the continuity of signal detection, including the identification of any possible change in the expected frequency of adverse reactions reporting or a change in trend that could indicate a new signal (in particular, as a consequence of introducing changes in the production process of a biological product). Certain active ingredients may be subject to more

frequent monitoring requirements; changes in the production process are grounds for special measures to ensure timely signal detection.

745. Signals from biological medicinal product data monitoring shall be assessed against serial exposure data, including batch numbers shipped or sold, batch size data, and regions (countries) to which batches were supplied. It is recommended to intensify routine pharmacovigilance processes to ensure timely detection of new risks and changes in the safety profile or quality of a biological medicinal product at any stage of the life cycle. For new signals, an assessment shall be made to extend this signal to the suspected biological medicinal product or all similar active ingredients. If there is insufficient data to confirm the specificity of the signal detected for a particular biological medicinal product, regulatory actions for all similar active ingredients, including the reference product, may be warranted to provide the required precaution for biological products. For any new identified clinical risk with an immunogenic etiology, a full study shall be performed to determine the relationship of this risk with a specific biological product or a specific batch of a biological product, and take measures to establish the cause of the detected clinical risk to implement further measures to minimize or eliminate this risk. (e. g., optimisation of control methods, stages of the production process).

7. Quality Requirements for Signal Management in Terms of Ensuring Traceability

746. Signal management is a critical process. Validation, prioritisation, evaluation, timelines, decisions, actions, plans, reporting, and other key procedures shall be properly documented and periodically monitored. Tracking systems shall also be documented and include cues that have led to the conclusion that there is no new potential causal link with a specific

biological medicinal product or a new aspect of a known relationship of such risk, as they may draw particular attention in the event of subsequent analysis. All records shall be archived and retained following applicable procedures.

8. Quality Systems and Documentation

747. An essential feature of the signal processing system is clear documentation to ensure the proper and effective functioning of the system, standardize responsibilities and required actions, perform these actions by appropriately qualified persons and understand them by all parties involved, implement proper control and (if necessary) improve the system. Based on these requirements, a quality assurance and quality control system shall be developed and applied to all signal management processes. Quality system procedures shall also be developed, documented, and implemented. This requirement applies to the methodology used and the frequency of work to detect signals.

It is necessary to assign roles and responsibilities regarding actions and documentation, control and investigation of quality issues, as well as taking corrective and preventive actions, including responsibilities for auditing quality assurance in the signal management system, including auditing subcontractors of contracting parties performing any work on this direction. Confidentiality of data and documentation, safety and reliability of data (including integrity during transmission) shall be guaranteed.

748. The traceability system shall ensure that data is retained by all parties involved at all signal management stages to create an audit trail that allows tracking and control of the detailed implementation of all stages of signal management, including assessment, analysis, decision making, and justification.

749. Roles and responsibilities for completing each stage of the activity, including record keeping, quality control, review, and taking corrective and preventive actions, shall be defined and documented.

750. The MA holder includes the description of the signal management process in the pharmacovigilance system master file. The system's effectiveness in terms of this process is subject to continuous monitoring; indicators of the process effectiveness are presented in an annex to the pharmacovigilance system master file. The MA holder must ensure that the document and records management system is in place for all processes of the pharmacovigilance system so that documents can be searched, all measures taken to investigate the safety concern can be tracked, and the deadlines for investigations and decisions regarding the safety concern (including dates and the decision-making process) are met. Regarding the signal management process, as with all other critical processes of the pharmacovigilance system, the MA holder shall ensure that regular audits are carried out, including when service providers and contract organisations are involved in this activity.

751. Documentation confirming the fulfillment of these requirements shall be available at any time, in particular if it is necessary to evaluate the evidence base for the actions taken and the decisions taken and the validity of such an assessment.

752. It may be necessary to review the MA holder's documentation of compliance with these provisions before and after the authorisation procedure to assess the activities performed or an inspection.

9. Personnel Training

753. Personnel shall be specially trained to perform signal processing activities according to the roles and responsibilities assigned. This requirement applies to personnel of the pharmacovigilance department, as

well as personnel who may become aware of potential signals or who are involved in signal processing, for example, personnel of the administrative (legal) department, personnel involved in preclinical, medical, pharmacoepidemiological and marketing research. Training shall include familiarity with the terminology and available databases of signal sources. Training system procedures and placement of training data shall be properly documented, personnel resumes and descriptions of their functions shall be archived.

10. Roles and Responsibilities

Role of the Member States' Authorised Authorities

754. The Member State's authorised authority performs the following actions:

a) controlling signal data on their own territory, including data obtained from other sources specified in paragraphs 704–707 of these Rules;

b) validation and other stages of the procedure for processing signals received from available sources;

c) submitting signals that have passed through the validation and assessment procedures to the relevant expert committees of the Member States to determine the feasibility of subsequent actions to further study the signal or minimize the risk;

d) information sharing with other authorised authorities of the Member States about the identified signals that have been validated and the measures developed.

Roles and Responsibilities of MA holders

755. The marketing authorisation holder carries out the following:

a) continuous monitoring of the medicinal product safety and information sharing with the Member States' authorised authorities of new information that may affect the conditions for authorisation, including emerging safety issues;

b) control of all available data and information on signals;

c) continuous data monitoring in adverse reaction databases and other sources of information on signals. Signal detection shall include their validation, considering the components of the information provided, specified in paragraphs 720–722 of these Rules;

d) validation of all detected signals and reporting to the authorised authorities of the Member States;

e) information sharing with the Member States' authorised authorities in case of identification of an emerging safety issue as a result of signal detection activities in accordance with paragraphs 756–757 of these Rules;

f) cooperation with the Member States' authorised authorities to implement signal assessment procedures by providing additional information upon request;

g) provision of an audit trail for all signal detection procedures;

h) ensuring that the medicinal product's information is consistent with the current scientific knowledge level, including the results of new safety information assessment by the Member State's authorised authorities.

11. Emerging Safety Issues

756. When receiving information on a medicinal product that meets the emergency safety criteria, a MA holder ensures that the Member States' authorised authorities in whose territory the given medicinal product is authorised are informed in writing or by e-mail. Information regarding an emergency safety issue shall be submitted as soon as possible, but no later

than 3 business days after it has been determined that the validated safety signal or safety concern meets the definition of an emerging safety issue. The reporting requirement for a detected emerging safety issue is in addition to the requirement for urgent submitting of individual case safety reports for cases where the emerging safety issue is related to a single case of a suspected adverse reaction.

757. When notifying of an emerging safety issue, the MA holder should include in the submission the issue description, the source of information, any action planned or taken with deadlines, and any documentation of this safety issue available at the time of the initial notification. The MA holder shall ensure that any additional information on the safety issue is submitted to the Member States' authorised authorities as soon as it becomes available.

758. Upon receipt of notification of an emergency safety issue by the Member State's authorised authority, an immediate assessment of the urgency and potential impact of the safety concern is carried out, and appropriate actions and possible regulatory measures are determined concerning the detected safety issue. Where it has been determined that the emerging safety issue meets the criteria for an incident, the Member State's authorised authority may carry out some additional consultations, involving the relevant competent organisations in order to assess and take appropriate measures to prevent a serious impact on public health (health of the population).

An incident may be related to quality, efficacy, or safety concerns, but most likely to the safety and/or quality issues (and possibly subsequent supply shortages). It must be taken into account that situations that are not initially assessed as serious for public health but become publicly available after media coverage or other information resources, and may lead to serious public concern about the medicinal product, may also need to be classified as emergencies. Likewise, other situations that may negatively affect the proper

use of medicines (e. g., situations leading to medication discontinuation) may be classified as an emergency.

An incident refers to a medicinal product authorised in the Eurasian Economic Union, regardless of the authorisation method.

759. The MA holder shall ensure effective interaction and cooperation with the Member States' authorised authorities at the stages of assessing an emergency safety issue.

760. To prevent unreasonable overload and ensure operational effectiveness, the MA holders should report only such emerging safety issues, i. e., where no delays in assessment and action are allowed due to their urgency and severity.

761. If, based on the results of an assessment of an emerging safety issue, the MA holder decides on one of the following measures: temporary or permanent suspension of the sale and use of the medicinal product, withdrawal of the medicinal product from the market, request for withdrawal of the marketing authorisation or refusal to apply for confirmation of the marketing authorisation, a notification of the adoption of these decisions or measures should be sent to the Member States' authorised authorities.

762. New safety information related to the medicinal product's non-compliance with quality requirements or the use of an adulterated medicinal product, which may affect the assessment of the risk–benefit ratio of the medicinal product and which may lead to a serious restriction in the supply of the medicinal product, is also not subject to submission to the Members States' authorised authorities as an emerging safety issue and is presented following the requirements of the Member States' legislation on providing information on deviations in the medicinal product's quality from the requirements established for this product's quality.

12. Monitoring of Common Information Database on Detected Adverse Drug Reactions (Actions), Including Reports on Medicinal Product Ineffectiveness

Procedure for Accessing the Adverse Reaction Database

763. The Member States' authorised authorities have access to all data elements of individual adverse reaction reports, which are included in the Common Information Database on Detected Adverse Reactions (Actions) to Medicinal Products, Including Reports of Medicinal Product Ineffectiveness (hereinafter referred to as the adverse reaction database).

764. The MA holders have access, without restriction, to all data items of individual case safety reports that have been submitted by the MA holder for inclusion in the adverse reaction database. For other individual case safety reports included in the adverse reaction database, MA holders may request access to the individual reports' expanded data elements, including adverse reaction case descriptions, with confirmation of confidentiality and use of the data on such reactions only for signal management work.

Monitoring Frequency

765. The MA holders and the authorised authorities of the Member States shall ensure continuous monitoring of the adverse reaction database. The monitoring frequency is determined in proportion to the identified risks, potential risks and the need to obtain additional information about the medicinal product or active ingredient.

766. The frequency of monitoring data in the adverse reaction database may change as data on a medicinal product's safety profile or active ingredient accumulates with due account for the following factors:

a) period of time from the date of the first authorisation;

b) the degree of impact on patients;

c) important potential risks and missing information (according to the risk management plan);

d) frequency of submission of the periodic safety update report;

e) the number of individual case safety reports received during a given period;

f) the presence of specific situations related to safety concerns (e. g., the vaccination campaign period).

767. MA holders shall determine the appropriate monitoring frequency for each of the active ingredients or medicinal products to meet monitoring obligations. The minimum recommended frequency for monitoring the adverse reaction database is 6 months. More frequent monitoring is carried out for active ingredients included in the list of medicinal products subject to additional monitoring unless the only reason for inclusion in the list was the requirement to perform a post-authorisation safety study. The frequency of monitoring, including changes to be made, and the frequency justification should be documented following the organisation’s internal procedures.

Analysis of the Adverse Reaction Database

768. The selection of the combination of drug and adverse reaction for the subsequent review of the data should be based on evidence-based factors (e. g., the number of cases matched by the statistic, data on the safety profile of the medicinal product, clinical significance, comorbid condition, population characteristics, and data from previous assessments). Not all cases of disparity in reporting are subject to further study. Particular detected combinations of the medicinal product and adverse reaction, for which disparity in reporting has not been determined, require further study with an assessment of the adverse reaction database.

769. The results of the adverse reaction database review contain information about the active ingredient or combination of active ingredients. Scientific evaluation of the data shall suggest determining the likelihood that the signal in operation can be characteristic for all or only for certain medicinal products containing a given active ingredient or a combination of active ingredients. In their analysis, the marketing authorisation holders shall take into account all individual adverse reaction reports related to the medicinal product safety.

770. When validating a signal, the analysis of information contained in the adverse reaction database shall be performed with account for previous knowledge of the signal, the degree of evidence for the relationship between the signal and the medicinal product, and clinical significance. Records management for monitoring and analyzing the database is performed following the organisation’s internal procedures.

The procedure for notifying the Member States’ authorised authorities by the holders of the marketing authorisation of the signals detected based on monitoring the adverse reaction database.

771. If a new signal is detected during monitoring of the adverse reaction database, the MA holder shall validate this signal and then inform the Member States’ authorised authorities.

772. Signal validation shall include a thorough analysis of the information contained in the adverse reaction database by the marketing authorisation holder. For validated signals, the analysis should be supplemented with assessment of other available data (e. g., from the MAH database, articles in the scientific medical literature, clinical trial data). The marketing authorisation holder, where possible, shall assess the distribution of information on the identified new risk to other medicinal products

containing a similar active ingredient (except for cases where the risk related to a particular medicinal product is identified). In this case, information on the medicinal product should be brought into line with the newly identified risk by making changes in the marketing authorisation conditions. The MA holder should also consider the information on signals published or being considered by the Member States' authorised authorities.

773. Based on own assessment, the MA holder can make the following conclusions regarding the signal:

a) the signal can be classified as rejected;

b) the signal is a new risk;

c) the signal represents a change in a previously known risk;

d) the signal assessment requires a subsequent analysis by the authorised authorities.

774. The starting point ("day zero") of the signal notification periods specified in this document is the conclusion that the signal is a new or changed risk and/or that further analysis by the authorised authorities is required.

775. The establishment of a new or changed risk, which requires a change in the marketing authorisation conditions, is the basis for applying to changing the marketing authorisation conditions if the MA holder does not believe that the subsequent analysis of the signal by the authorised authorities is justified. Subsequent analysis by the authorised authorities may be requested if the validated signals, based on the MA holder's assessment, can neither be refuted nor confirmed as new or changed risks.

776. Informing about signals requiring further analysis by the authorised authorities can only be carried out as part of a periodic safety update report if the conditions specified in paragraphs 782–784 of these Rules are met. Where the above conditions are not met, the MA holder shall

send a separate notification of the signal to the Member States' authorised authorities in accordance with paragraphs 785–788 of these Rules.

777. Notification of rejected signals to the Member States' authorised authorities is sent only through the inclusion of this information in the periodic safety update report.

778. The Member States' authorised authorities are informed about validated signals requiring immediate attention as part of the procedure for notification of an emerging safety issue in accordance with paragraphs 756 and 757 of these Rules.

13. Changing the Conditions of the Marketing Authorisation

779. Based on his own assessment of the detected signal when monitoring the adverse reaction database, the MA holder can conclude the need to make changes in the information on the medicinal product and/or the risk management plan due to obtaining new data. In such cases, the MA holder should apply for changing the marketing authorisation conditions to the relevant authorised authorities as soon as possible but no later than 3 months after the signal assessment completion which has provided the grounds for assessing the signal as meeting the definition of an important risk, or within 6 months in the case of adverse reactions or risks that are not considered an important one.

780. In the cases, specified in paragraph 779 of these Rules, a separate notification of the signal in accordance with paragraphs 785–788 of these Rules is not required since the authorised authorities will assess the proposed changes and the corresponding evidence base as part of the procedure for changing the marketing authorisation conditions.

781. MA holders should comply with the requirements of the Union authorised authorities' legal acts in terms of changing the marketing

authorisation conditions and, in appropriate cases, coordinate with the authorised authorities on issues related to preparing an application for making changes.

14. Including a Signal in a Periodic Safety Update Report

782. Where the frequency of submitting a periodic safety update report for the active ingredient of a medicinal product is 6 months after the MA holder completes assessment of the signal identified as a result of continuous monitoring of the adverse reaction database, it is not required to submit a separate notification of the signal to the Member State's authorised authority in accordance with paragraphs 785–788 of these Rules. Where the MA holder has completed the evaluation of the signal after the date of the closure of the databases, information on this signal should be included in the section of the periodic safety update report "Important Information Received on Completion of the Periodic Safety Update Report Preparation" along with the proposal for further signal management.

783. Based on an evaluation of the cumulative safety data and the risk–benefit ratio analysis provided in the periodic safety report update, the MA holder shall conclude the need to change the conditions of the marketing authorisation and/or take action, including any changes to the approved medicinal product information for the product for which the periodic safety update report has been submitted. This also applies to conclusions based on the safety signal assessment.

784. Regardless of the source of information on the signal, the periodic safety update report includes information on all validated alarms and emerging safety issues that were assessed during the reporting period or after the closure of the databases.

15. Special Signal Notification

785. Where the performed assessment of the signal detected by monitoring the adverse reactions database allows the MA holder to conclude that this signal does not comply with the requirements of paragraphs 779–784 of these Rules and subsequent analysis of the signal by the Member States' authorised authorities is required, the MA holder should fill out the special signal notification form available on the web portal of the Member States' authorised authorities and send the notification form to the Member States' authorised authorities of in which the corresponding medicinal product is approved.

786. Special notification of the signal shall be sent as soon as possible, but no later than 30 calendar days after the MA holder has completed the assessment and concluded the need for analysis by the Member States' authorised authorities.

787. Special notifications about the signal are not required if the signals are included by the MA holder in the periodic safety update report or are the basis for initiating the procedure for changing the marketing authorisation conditions in accordance with the provisions of paragraphs 779–784 of these Rules.

788. Information on signals rejected by the MA holders based on the assessment should not be sent to the Member States' authorised authorities in the form of special notifications about the signal. Information on these signals should be included in the periodic safety update report.

16. Subsequent Regulatory Processes

789. Where the Member States' authorised authority decides on the need for additional actions, this authorised authority assess the signal and

agrees on the follow-up actions in relation to the marketing authorisation within a time frame proportionate to the safety concern degree and severity; thereafter, the following decisions can be made:

the MA holder shall provide additional data for the assessment as part of the procedure being performed;

the MA holder shall conduct an additional assessment of the data and submit such an assessment within the established time frames;

the MA holder shall perform a review of additional signal data and include its results in a regular or unscheduled periodic safety update report;

the MA holder shall bring the medicinal product information in line with the new information by making changes in the authorisation conditions;

the MA holder shall ensure financing and conducting of a post-authorisation study following the agreed protocol and provide the final results of such a study;

the MA holder shall submit a risk management plan (with account for new information);

the MA holder shall take additional risk minimisation measures required to ensure the safe and effective use of a medicinal product (e. g., as part of an educational program or by direct provision of information to healthcare professionals);

the authorisation status is subject to change, the validity of the marketing authorisation certificate shall be suspended or not renewed, the marketing authorisation certificate shall be revoked;

urgent safety restrictions shall be imposed.

authorised authorities of the Member States need to collect additional information (e. g., through the pharmacovigilance data exchange system) or perform additional analysis of the available data;

authorised authorities of the Member States need to obtain additional scientific consultation from other expert committees;

it is necessary to carry out an unscheduled inspection of the pharmacovigilance system to confirm that the MA holder complies with the pharmacovigilance system's requirements established by legal acts of the Union authorities of and the Member States' legislation;

it is necessary to include the suspected medicinal product in the list of products subject to additional monitoring;

other additional steps shall be taken;

no additional assessment or action beyond routine pharmacovigilance is required.

Recommendations of the Member States' authorised authorities based on the assessment results of signals are subject to publication on the Member States' authorised authorities' official website on the Internet.

17. Management of Records in the Safety Concern Tracking System of the Member States' Authorised Authorities

790. The Member States' authorised authorities ensure that information on the following signals is entered into the safety concern tracking system:

a) signals in respect of which the Member State's authorised authority carried out the validation procedure;

b) validated signals, information about which was received from the MA holders;

c) emerging safety issues.

791. Information on signals in the safety concern tracking system of the Member States' authorised authorities includes the following elements:

a) description of the validated signal;

b) grounds for rejection (for rejected signals);

c) a report on the signal assessment, the time frame for the procedure stages, the recommendations of the expert committee (for confirmed signals).

18. Openness of the Authorised Authorities' Decisions

792. The Member States shall monitor the timeliness of communication to the population of important safety concerns identified by the pharmacovigilance system through publication on the Member States' authorised authorities' websites on the Internet and other available means of communication.

X. Post-Authorisation Safety Studies

1. General Provisions

793. A post-authorisation safety study of a medicinal product may be initiated, controlled, or financed by the MA holder on his/her own initiative or in accordance with the obligation imposed on him/her by the Member States' authorised authority as a condition for issuing a certificate of marketing authorisation or after the issuance of a certificate of marketing authorisation, if there is an assumption that there are risks associated with the authorised medicinal product requiring additional study by conducting a research.

794. A post-authorisation safety study may be a clinical trial or a non-interventional study, including with the use of data from real clinical practice.

795. The requirements of this section are applicable to non-interventional post-authorisation safety studies in the Member States territories.

796. A post-authorisation safety study includes a study that collects data from patients and healthcare professionals and studies that reuse data

previously obtained for another purpose and stored in patients' medical records or other documents (including in electronic format).

797. Where the post-authorisation safety study is a clinical trial, it shall comply with the requirements stipulated by the Union authorities' legal acts and the Member States' legislation for arranging and conducting clinical trials.

798. The primary objective of a non-interventional post-authorisation safety study shall include obtaining some scientific evidence of potential clinical or public health significance.

799. The objectives of a post-authorisation safety study may include:

a) quantifying potential or identified risks (e. g., assessing the frequency of occurrence, relative risks compared to such risks in a population that has not used a given medicinal product or a population that has used another medicinal product or class of medicinal products, as well as examining risk factors and factors that modify the effect of the medicinal product);

b) risk assessment of a medicinal product used for approved indications in patient groups that have not been studied or have been insufficiently studied at the pre-authorisation stage (e. g., pregnant women, special age groups, groups of patients with renal or hepatic impairment);

c) assessing the risk arising from the long-term use of a medicinal product;

d) confirming the absence of risks associated with the medicinal product administration;

e) assessing the standard medical practice of medicinal product prescription with obtaining additional information on the safety of products or the effectiveness of risk minimisation measures (e. g., collection of information on use according to indications, use not following the summary

of product characteristics, concomitant therapy, medication errors in routine medical practice that may have an impact on the safety profile; and studies to obtain data to assess the safety impact on public health (health of population));

f) assessing the effectiveness of risk minimisation measures.

800. The design of a post-authorisation safety study shall correspond to the purpose of the study; while, a study's classification as a post-authorisation study is not limited to the type of design chosen if it meets the above criteria. For example, a systematic review of the scientific medical literature or a meta-analysis may be considered a post-authorisation safety study (depending on the research objective).

801. MA holders shall consider the relevant scientific guidelines in developing study protocols, conducting the study, and compiling study reports. When assessing study protocols and study reports, the Member States' authorised authorities should also take into account such guidelines and methodological standards in the field of pharmacoepidemiology.

802. For MA holder-sponsored post-authorisation safety studies, if designed, conducted and fully or partially reviewed by investigators who are not employees of the MA holder, the MA holder shall ensure the necessary qualifications, training and experience of the investigators.

803. The agreement concluded between the MA holder and the researchers shall ensure the fulfillment of regulatory obligations during the study and the scientific examination of the data obtained, contain conditions that determine the methodological standards implementation for conducting pharmacoepidemiological studies and provide for the following aspects that are important for the study arrangement and conduct:

a) justification, main objectives, and a summary of the planned study methods;

b) rights and obligations of the investigator and the MA holder;

c) tasks and responsibilities of the parties;

d) procedure for obtaining an agreement on the study protocol;

e) procedures to ensure that the MA holder fulfills its pharmacovigilance obligations, including urgent reporting of adverse reactions and other safety data (where applicable);

f) intellectual property rights arising from study and access to study results;

g) storage and access to the data set for analysis and the statistical programs used to process the data for auditing and inspecting the study;

h) strategy for informing about the stages of the study and the preparation of the final report;

i) strategy for publishing interim and final study results.

804. A non-interventional post-authorisation study shall not be performed to promote the medicinal product on the market. This requirement applies to all studies and all activities carried out within the study, including both studies carried out by the MA holder’s personnel and those performed with the participation of third-parties.

805. Payment for the participation of healthcare professionals in the study shall be limited to reimbursement of the time and costs required to complete the study.

2. Registration of the Study

806. Non-interventional post-authorisation safety studies, the conduct of which is part of the MA holder’s obligations established by the Member State’s authorised authority, are subject to registration in the electronic register of post-authorisation studies of the Member States (hereinafter referred to as the register) posted on the website of the relevant Member

State’s authorised authority on the Internet. The date of registration of the post-authorisation study in the registry is taken as the check date of submitting the final report on the study results.

807. To ensure transparency of all non-interventional studies performed and sharing the pharmacovigilance data between the Member States’ authorised authorities and MA holders, the MA holders should ensure that the information on all non-interventional post-authorisation safety studies performed in the Member States territories and provided for by the risk management plans agreed with the Member States’ authorised authorities or carried out on their own initiative is entered in the register.

808. Non-interventional post-authorisation studies are subject to registration in the register before starting the study or at an earlier date (e. g., if data collection as part of the study agreed in the risk management plan has been started). The study protocol is subject to inclusion in the register before starting the collection of data on the study or at an earlier date. Information on significant changes in the study protocol, reports on the study progress and the final study report shall be included in the register no later than 14 calendar days from the date of completing the preparation of these documents. Information on the study is presented in Russian (preferably). If the study protocol is drawn up in English, the MA holder translates the study’s name, the summary of the study protocol, and the summary of the final study report into Russian.

809. Where the protocol pre-publication could adversely affect the study credibility (e. g., in relation to studies with primary data collection where prior knowledge of the study objectives may lead to errors) or protection of intellectual property rights, such a protocol may be submitted or revised by the MA holder directly to the registry before collecting the data. This version of the protocol shall be justified and contain the minimum

required amount of information, including in cases of editing. The title page of the protocol shall include a mark indicating the protocol version. In this case, before collecting the data, the MA holder provides the complete study protocol at the request of the Member State's authorised authority. The full study protocol shall be placed in the registry no later than 14 calendar days from the data lock point.

3. Study Protocol

810. Non-interventional post-authorisation safety studies performed by the MA holders in all cases (both in accordance with the obligations imposed by the authorised authorities, and on their own initiative) shall be carried out in accordance with a scientifically justified study protocol developed by persons with appropriate qualifications and experience.

811. When conducting post-authorisation safety studies on its own initiative, the MA holder should, before collecting the data, submit the study protocol to the Member State's authorised authority in whose territory the study is planned.

812. For post-authorisation safety studies initiated by the MA holder following the obligation imposed by the authorised authority of the Member State, the MA holder shall ensure that before collecting data, the information about the research, including the draft study protocol, is submitted to the Member State's authorised authority, which has been obliged to conduct post-authorisation safety studies before collecting the data. In the case of post-authorisation safety studies in the territory of other Member States, it is necessary to inform the authorised authorities of these Member States of these studies and submit the study protocol.

813. For the MA holder to fulfill his obligations to carry out pharmacovigilance activities, the authorised pharmacovigilance officer, or the

person to whom the relevant powers have been delegated, shall be involved in the review and approval of protocols of studies carried out by the MA holder following the obligations imposed by the authorised authorities under the agreed risk management plan, or on own initiative. A contact pharmacovigilance person at the Member State level shall be informed of any post-authorisation safety study conducted or sponsored by the MA holder in the Member State concerned and shall be provided with an access to the study protocol.

Format and Content of the Test Report

814. The protocol of a post-authorisation safety study performed by the MA holder in accordance with the obligation imposed by the authorised authority under an agreed risk management plan or on its own initiative shall contain the following sections:

a) name of post-authorisation safety studies (full and contracted one (abbreviation)), including commonly used terminology, defining the study design and the investigational medicinal product, the active ingredient or group of the investigational product, containing a subtitle with an indication of the version and the last revision date. Once the study protocol is registered in the registry, its subsequent versions shall contain the number of the post-registration safety study in accordance with the registry);

b) MA holder (name and location (address) of the MA holder);

c) responsible parties (names, positions, qualifications, places of work (addresses) and details of all responsible parties, including the main author of the protocol, principal investigators, coordinating investigators for each Member State and research centers where the study is to be conducted, and as well as other information related to the sites where the study is being conducted. A list of all institutions and researchers involved in the study

should be available upon request from the Member States' authorised authorities);

d) summary (a separate summary of the study protocol), including the following subsections:

name of the study (with subtitles), indicating the version and date of the protocol, as well as the last name, first name and patronymic (where available) of the protocol author, information about the protocol author's main place of work;

justification and prerequisites for conducting the study;

purpose and objectives of the study;

study design;

study population;

monitored indicators;

data sources;

study size (sample size);

data analysis;

main study stages;

e) changes and updates (information about a significant change in the study protocol upon starting the data collection, including the justification and date of each change, as well as a link to the section of the protocol in which the change was made);

f) milestones (data in tabular form) with planned dates for completing the main study stages and reporting:

start of data collection;

data lock point;

study progress reports;

interim reports on the study results (where applicable) following the data analysis stages;

final report on the study results.

Data shall be provided for any other important study stages.

g) justification and background (description of the safety concern(s), safety profile, or risk management measures that became the grounds for conducting the study, as well as a critical analysis of all available published and unpublished data assessing relevant safety information or an indication of the missing safety knowledge that the study is designed to obtain. The review may include results from relevant animal experiments, clinical trials, population statistics, and data from previous epidemiological studies. The review should contain references to the results of similar studies and information about the significance of this study in knowledge of the medicinal product safety);

h) study purpose and objectives (the purpose of the study, explaining how the study will contribute to the solution of the question that led to its initiation, and the objectives of the study, including any preliminary hypotheses and main theses describing the information or data that shall be obtained in the study);

i) study methods description, including the following:

study design (description of the study design and the justification for its selection);

study conditions (study population, defined in terms of person, place, time period, and sampling criteria, including the justification for any inclusion and non-inclusion criteria applied. If any sample is taken from the target population, a description of the target population and the sampling methods' details are required. If the study design is a systematic review or meta-analysis, an explanation of the selection criteria and study suitability is needed).

j) variables (outcomes, impacts, and other variables, including measurable risk factors with a characterisation of each separately; potential factors that distort outcomes and effect-modifying factors, including operational definitions);

k) data sources (the strategy and data sources for identifying impacts, outcomes, and all other relevant variables to the study objectives, such as potential bias factors and effect-modifying factors. A description of the validation method is required when using validated data sources, instruments, and measurements. If methods for obtaining data or tools are being tested in a pilot study, the pilot study plans should be submitted. A description of all expert committees involved and the assessment procedures used to validate the diagnoses should be provided. If an existing data source, such as an electronic health record, is used in a study, any information regarding the validity of the records and the data's coding shall be indicated. In the case of a systematic review or meta-analysis, it is necessary to describe the study strategy and processes and any methods to confirm the investigators' data);

l) sample size (the planned sample size, the planned accuracy of the study results, and the calculation of the sample size minimizing the predetermined risk with a predetermined power);

m) data management (data management and statistical software and hardware used in the study, including procedures for collecting, recovering, and preparing data);

n) data analysis (all the critical stages from raw data to final output) the methods used to correct inconsistencies or errors, invalid values, modify raw data, categorize, analyze and present results and procedures to control sources of biases and their effect on results, any statistical procedures applied to the data to obtain point estimates and confidence intervals for frequency of occurrence or relationship measurements, and any sensitivity analysis.

Primary analysis shall be clearly distinguished from subgroup analysis and secondary analysis);

o) quality control (description of mechanisms and procedures to ensure the data quality and integrity, including the accuracy and readability of the received data and primary documentation, information on record keeping and archiving of statistical programs, description of available data on validation of record verification procedures and validation of endpoints, includes data the certification and/or qualifications of any supporting laboratory or research groups (where applicable);

p) limitations on study methods (limitations on study design, data sources and analytical methods, including problems of confounding results, errors, generalisation and random error, efficiency forecast of the success of measures aimed at reducing errors);

q) protecting study subjects (safety measures to ensure compliance with a Member State’s legislation in terms of observing the rights of participants in non-interventional post-authorisation safety studies);

r) data management and reporting of adverse events and adverse reactions (procedures for collecting, managing, and reporting individual cases of adverse reactions and any new information that may affect the assessment of the risk–benefit ratio of a medicinal product during the study);

s) plans for distributing the findings and communicating the study results, including plans for submitting ongoing reports, final reports, and publications.

815. For studies involving the primary collection of data, if certain adverse events are excluded from the volume of data collected, the MA holder shall justify the approach to safety data collection used in this post-authorisation safety study in the study protocol. The indication of adverse events excluded from the collected data shall be provided using the MedDRA

dictionary’s appropriate level. If some of the safety information is excluded from the information collected as part of the study, this section of the protocol for healthcare professionals and patients shall include the contact details of the MA holder or the authorised authority and special forms shall be designed to submit information on adverse reactions. Where a suspected adverse reaction that resulted in a fatal outcome is not immediately reportable in the form of an individual adverse reaction report, information about such an adverse reaction shall be included in the list of such adverse reactions with the indication of the level of the system organ class in accordance with the MedDRA dictionary and grounds for exclusion of this case from the procedure for immediate reporting.

816. For studies based on the collection of secondary data, the relevant part shall describe the analysed adverse events or adverse reactions using the appropriate level of the MedDRA dictionary. When a study is performed using secondary data, the procedure for reporting suspected adverse reactions in the form of individual case safety reports is not required.

817. When performing a study with a combined design, the requirements for studies based on primary data collection shall be applied to adverse reactions for which information is obtained through primary data collection, and the requirements for studies based on secondary data collection shall be applied to adverse reactions for which information is obtained through secondary data collection.

References.

818. The section can include any additional information about specific aspects that were not previously considered (e. g., questionnaires, reporting forms).

819. Information about studies to assess the feasibility of studies conducted to support the development of the protocol (e. g., testing questionnaires or simple calculations of medical events or prescriptions from a database to determine the study's statistical accuracy) shall be posted in the appropriate section of the study protocol with a summary of their methods and results. The MA holder shall submit full reports at the request of the Member State's authorised authority. Such studies shall be fully described in the protocol (e. g., a pilot study of the patient questionnaire being used).

4. Control over Changes to the Study Protocol

820. Significant changes to the study protocol shall be made as needed during the study. Once the study has started, any significant changes to the study protocol shall be recorded in the protocol, specifying the change date, and traceability of the changes shall be ensured. Where the significant changes in the protocol have led to the recognition of the study as an interventional clinical trial, a subsequent study is carried out following the legal acts of the Union authorities.

821. For voluntarily initiated post-authorisation safety studies, the MA holder transfers the study protocol with changes or updates to the Member State's authorised authority, in the territory of which the post-authorisation non-interventional safety study of a medicinal product is being conducted.

822. For post-authorisation safety studies initiated by the MA holder following the obligation imposed by the Member State's authorised authority, the MA holder shall provide information on the introduction of any significant changes to the study protocol to the Member State's authorised authority, which were obliged to conduct post-authorisation safety studies before their introduction.

5. Submission of Pharmacovigilance Data to Authorised Authorities of the Member States.

Data that are Significant for Assessing the Risk–Benefit Ratio of a Medicinal Product

823. The MA holder monitors the data obtained during the study and assesses their impact on the respective medicinal product's risk–benefit ratio. Any new information that may affect the risk–benefit ratio assessment of a medicinal product is immediately communicated to the Member States' authorised authorities, in whose territory the post-authorisation safety study is conducted and the investigational product is authorised, in the form of an emerging safety issue report. Data that may influence the assessment of the risk–benefit ratio of a medicinal product may include data obtained from the analysis of information on suspected adverse reactions or the results of an interim analysis of pooled safety data.

824. Information on the studies' results as part of a periodic safety update report and in the risk management plan updates (where applicable) is presented regardless of the reporting procedures specified in paragraph 823 of the Rules.

Suspected Adverse Reactions and Adverse Events that Should Be Reported Urgently

825. Information on serious unforeseen adverse reactions shall be submitted urgently to the Member States' authorised authorities in accordance with the requirements of Section VII of these Rules.

826. Information on adverse reactions and adverse events obtained during primary data collection studies should be documented and summarised in the interim safety data analysis report and the final study report.

827. Information on adverse reactions and adverse events obtained during studies with secondary data collection shall be documented and summarised in the interim report on the analysis of safety data and the study protocol's final report unless the study protocol provides for and justifies a different procedure for presenting safety information.

828. Procedures for collecting information on adverse reactions and events, including data management (along with review and assessment by the MA holder where applicable), and reporting of the said adverse reactions and events shall be performed at the clinical study site and summarised in the study protocol.

6. Study Progress Report and Interim Study Results Report

829. The study progress report contains information that reflecting the stage of the study, for example, the number of patients included in the study who were exposed to a medicinal product or the number of patients with a monitored outcome, and problems and deviations from the expected study design. The study progress report may include interim data from the study results.

830. An interim study report contains the results of the planned interim analysis of study data before or after the data lock point.

831. The Member State's authorised authority may request the submission of a report on the progress of the post-authorisation safety study, which is obligatory for the MA holder or is carried out voluntarily in the Member State territory. Requests for study progress reports may be made before the start of the study or during the study. The request may be information regarding the efficacy and/or safety profile that arises during the study or the need to obtain information about the study's progress related to

the procedures provided for by the Union law and the Member States' legislation, as well as important information on the medicinal product safety.

832. The time for the interim report submission shall be agreed upon with the Member States' authorised authorities and indicated in the study protocol where the procedure for submitting reports was agreed on before the study started. The post-authorisation safety study's progress shall be reflected appropriately in a periodic safety update report and risk management plan updates (where applicable).

833. After considering the study progress report by the Member State's authorised authority, additional information may be requested.

7. Final study report

834. The final report of a non-interventional post-authorisation safety study initiated by a MA holder according to an obligation imposed by the Member State's authorised authority shall be submitted with the Member State's authorised authorities as soon as possible after its completion and within 12 months of the data lock point.

835. For post-authorisation safety studies initiated by the MA holder, the final study report should be submitted to the Member States' authorised authorities on whose territories the medicinal product is authorised.

836. Should the study be terminated, a final report is submitted with indication of the reason.

837. The final report of the post-authorisation safety study should include the following information:

a) name: a name that includes common terminology and indicates the study design, the final report date, last name, first name, patronymic (if any) of the report author. Should the study be registered in the Member States' registry of post-authorisation safety studies, the authorisation number and a

link to the posted records of the study on the web portal of the Member States' authorised authorities should be indicated;

b) a summarised content, including the following:

information about the study title and subtitle, indicating the version number, the protocol approval date, the surname, name and patronymic (if any) of the main author with indication of the place of his/her work;

justification for the study;

research question and research objectives;

study design;

study population;

variables under study;

data sources;

sample size;

data analysis;

control points;

c) the MA holder: the MA holder's full name and his/her location (address);

d) researchers: surname, name, patronymic (if any) titles, degrees, places of work (addresses), and details of all researchers, and a list of all organisations and locations involved in the study. This information is provided by each Member State where the study was conducted and shall be available upon request from the Member States' authorised authorities;

e) control points (dates of the study control points):

start of data collection (planned and actual);

data lock point (planned and actual) or date of the study termination (where applicable) with reasons;

study progress report;

interim study results report (where applicable);

final report on the study results;

other control points applicable to the study, including the date of approval of the protocol by the ethics committee (where applicable) and the date of the study registration in the electronic study registry.

f) justification and background for the study: a description of the safety concern that led to the study conduct and a critical analysis of all available published and unpublished data assessing relevant safety information or an indication of the study's missing safety information was designed to acquire;

g) the purpose and objectives of the study, including preliminary hypotheses in accordance with the study protocol;

h) changes and updates: a list of any significant changes and updates to the original test report after the start of data collection, including the justification for each change or update;

i) study methods, including the following:

study design: key elements of the study design and the justification for the design selected;

conditions: conditions, location, and relevant dates of the study, including periods of enrollment, follow-up, and data collection (in the case of a systematic review or meta-analysis, characteristics of studies used as acceptance criteria, with their justification);

patients: target population and criteria for enrolling patients in the study. The sources and methods of recruiting the participants, including (where applicable) their detailed description, as well as the number of participants who dropped out of the study and the reasons for dropping out of the study, shall be indicated;

variables under analysis: outcomes, effects of the medicinal product, prognostic factors, potential confounding, and effect-modifying factors, including operational definitions and diagnostic criteria, where applicable;

data sources and measurement: for each indicator under consideration, the data sources and details of the estimation and measurement methods (if applicable) and the comparability of estimation methods (if more than one method is available) are indicated. Where the study has used an existing data source (electronic health records), any information about the records validity and data coding should be included in the report. In the case of a systematic review or meta-analysis, all sources of information, search strategy, methods for selecting studies, methods for extracting data, and processes to obtain and confirm data shall be described;

errors: a description of the action or steps taken to deal with potential sources of error;

sample size: the sample size and the justification for any calculation of the sample size and method to achieve the estimated sample size;

data transformation: transformations, calculations, or operations with data, including processing quantitative data when performing analysis, the justification of the selected methods of grouping data;

statistical methods (description by the following aspects):

basic methods of generalisation;

all statistical methods used in the study, including methods for controlling bias (concerning meta-analyses, methods for combining study results);

any methods used to study subgroups and interactions;

approach to solving the problem based on unavailable data;

assessment of the study sensitivity;

all changes to the data analysis plan provided for by the study protocol, with the justification of the changes;

quality control: mechanisms and procedures to ensure the quality and integrity of data;

j) results: presentation of tables, graphs, and illustrations to display the data obtained and the analysis performed. Both adapted and non-adapted results shall be presented. The assessment of the accuracy of the data shall be performed quantitatively with confidence intervals. This section should include the following subsections:

participants: number of patients at each stage of the study (e. g., number of potentially eligible, screened, assessed as eligible for inclusion, enrolled, completed, and reviewed, and reasons for dropping out of the study at any stage). Where a systematic review or meta-analysis is conducted, indicate the number of patients screened, assessed for compliance and included in the systematic review or meta-analysis, specifying the reasons for withdrawal from the study at each stage;

descriptive data: characteristics of study participants, information on patient exposure to the medicinal product and potential data corrupting factors, and the number of participants with missing data for each variable analysed. When conducting a systematic review or meta-analysis, the data (sample size, planned study) used for the study are indicated;

data on results: number of participants by categories subject to the main results obtained;

main results: inadaptive evaluation results (where applicable), the adjusted estimate for confounding factors, and their accuracy (e. g., 95% confidence interval). Where applicable, the relative risk assessment shall be translated into absolute risk for a significant period of time.

other analyses: other analyses performed, such as subgroup and interaction analyses and sensitivity analyses;

adverse events and adverse reactions: data management and reporting of adverse events and adverse reactions to the Member States' authorised authorities in accordance with the requirements of Section VII of these Rules.

For certain study designs, such as case–control or retrospective cohort studies, those involving analysis of electronic medical record data, systematic reviews, and meta-analyses, it should be stated that it is impossible to assess the reliability degree of the causal link at each individual case level;

k) discussion:

main findings: results relevant to the study objectives, results from a previous study that agree or disagree with the results obtained in this study, as well as their impact on the risk–benefit ratio of the medicinal product (where applicable);

limitations: limitations of the study subject to the circumstances that could affect the quality and integrity of the data, limitations of the approach, and methods that were used to minimize their impact (e. g., response rate, missing or incomplete data, estimated values applied), sources of potential errors and inaccuracies and the validity of events. It is necessary to discuss with the authorised authority (expert organisation) both the direction and the scale of potential errors;

interpretation: interpretation of study results considering objectives, restrictions, multiple analyses, results from similar studies, etc.;

generalizability of research results (external validity);

l) links;

m) other information about specific aspects of the study, not previously considered.

838. The summary of the final study report shall include a summary of the methods used in the study and the results obtained, being presented in the following format:

a) name of the study (as a title with subtitles), including the date of the summary, surname, name, patronymic (if any) and information about the first author from the group of authors;

b) keywords (no more than 5 keywords reflecting the main characteristics of the study);

c) justification and prerequisites;

d) purpose and objectives of the study;

e) study design;

f) conditions for conducting the study;

g) patients and sample size;

h) variables and data sources;

i) results;

j) discussion (including (where applicable) an assessment of the study's effect on the risk–benefit ratio of a medicinal product);

k) conclusion;

l) the marketing authorisation holder carries out the following:;

m) surname, name, patronymic (if any) and information about the principal investigator.

7. Study Results Publication by the Authors

839. The MA holder agrees in advance with the principal investigator on the publication strategy if the study is conducted and analysed in whole or in part by investigators who are not part of the MA holder. The MA holder shall be authorised to review research findings and interpretations included in materials to be published, and to submit comments prior to going to press, avoiding undue delay. Requests for changes to the materials to be published shall be scientifically established.

Submission of Published Study Results to the Member States' Authorised Authorities

840. To enable the authorised authority to get familiarised with the study data planned for publication in advance, the MA holder should submit the final version of the article to the Member States' authorised authorities in whose territory a medicinal product is authorised within 14 calendar days from the date the materials have been accepted by the publishing house.

8. Data Protection

841. MA holders and investigators shall comply with the legislation of the Member States in whose territory the study is being conducted to protect the privacy of patients. The MA holder shall ensure that all information on the study is properly handled and stored in such a way as to ensure the accurate transmission, interpretation and verification of this information. At the same time, the confidentiality of patient medical records shall not be violated.

9. Conducting Audits and Inspections

842. The MA holder shall ensure that his pharmacovigilance obligations are met concerning the study and provide the possibility of auditing, inspection, and verifying these obligations. Any changes to the data shall be documented to ensure that such changes are traceable in the documents. The MA holder shall ensure that the analytical data and statistical programs used to generate the final study report's data are electronically stored and made available for audit and inspection.

10. Impact on the Risk Management System

843. Information on a non-interventional post-authorisation safety study carried out in accordance with the obligations established by the Member State's authorised authority or on initiative according to the risk management plan shall be included in the MA holder's risk management plan.

844. In case there is no risk management plan, a new plan shall be developed, including the post-authorisation safety study data. All relevant sections and modules of the risk management plan are changed accordingly to reflect the study, including the safety specification, pharmacovigilance plan and risk minimisation plan, and an overview of risk minimisation measures.

11. Procedure for Mandatory Post-Authorisation Safety Studies

845. In the Member States, a post-registration safety study may be ordered by the Member State's authorised authority while assessing the application for authorisation or at the post-registration stage, where there are any grounds (reasonable expert opinion on the lack of important data characterizing the medicinal product's safety profile, whose receipt requires the implementation of active safety study methods due to the inability to properly study or assess the risk (risks) using routine pharmacovigilance methods) to suggest that conducting a post-authorisation safety study can have a significant impact on the risk–benefit ratio of the medicinal product.

846. This requirement of the authorised authority shall be properly justified by the assessment data of the safety and efficacy profile, shall be recorded in writing, and shall include the objectives and time frames for conducting the study. The requirement may also include recommendations for the study's key characteristics (e. g., study design, conditions, exposure to the

medicinal product, study outcomes, target population). Recommended methods may include active monitoring methods (e. g., monitoring at specific clinical sites, prescription monitoring, registries), comparative observational non-interventional studies (e. g., cohort study (monitoring), case–control study, case series study, etc.), clinical trials, consumption studies, pharmacoepidemiological studies.

847. Within 30 calendar days after receiving written notification from the authorised authorities about the appointment of a mandatory post-authorisation safety study at the post-authorisation stage, a MA holder has the right to request the possibility of submitting written comments regarding establishing an obligation to conduct a safety study of a medicinal product. The authorised authorities of the Member States determine the deadlines for submitting these comments. Based on the analysis of these written comments submitted by the MA holder, the Member State's authorised authority shall withdraw or confirm the obligation. Where the obligation is confirmed, the conditions for issuing a marketing authorisation shall be changed accordingly, and an instruction shall be provided to conduct a post-authorisation safety study as an obligatory condition for authorisation. Where there is a risk management plan, the MA holder changes the relevant sections of the plan.

12. Control over Non-Interventional and Post-Authorisation Safety Studies

Role and Responsibilities of the MA holders

848. The MA holder is responsible for ensuring that the study meets the criteria for a non-interventional post-authorisation safety study.

849. As regards the non-interventional post-authorisation safety study, the MA holder shall ensure that its pharmacovigilance obligations are met and that it can be audited, inspected and verified.

850. When the MA holder is obliged to conduct a non-interventional post-authorisation safety study, the MA holder must ensure the development of the study protocol with subsequent submission for assessment to the Member State's authorised authority. The MA holder is responsible for ensuring that the study meets the criteria for a non-interventional study at all stages of its execution.

851. A non-interventional post-authorisation safety study can be started only after receiving written approval from the Member State's authorised authority in whose territory the study is planned to be carried out. Approval by the authorised authority shall be based on ensuring the well-being and protection of study participants' rights.

852. Upon agreeing on the post-authorisation safety study protocol, the MA holder shall ensure that all subsequent planned significant changes to the post-authorisation safety study protocol are submitted to the authorised authority before the start of their introduction.

853. Upon completion of the study, the MA holder submits the final report on the study, including the summary of the final report for publication, to the authorised authority of the Member State as soon as possible, but no later than 365 calendar days (12 months) after the data lock point, if the Member State's authorised authority does not write permission was granted to extend the time period for the report submission. A request for the possibility of extending the deadline for submitting the final report must be sent by the MA holder to the Member State's authorised authority no later than 3 months before the deadline for the mandatory report submission.

854. The MA holder is responsible for carrying out a proper assessment of the study results, their impact on the conditions of authorisation and submission (where necessary, to the Member States' authorised authorities) of an application for changing the authorisation conditions.

Authorised Authorities of the Member States

855. After receiving the authorised authorities' decision on the appointment of a non-interventional post-authorisation safety study, the MA holder develops a study protocol and submits it for consideration by the Member State's authorised authority. Within 60 calendar days from the date of submission of the draft protocol, the Member State's authorised authority prepares a response, containing the following information:

approval of the draft study protocol;

recommendations for making changes to the study protocol;

refusal to agree on the study protocol or notification of the MA holder that the study is clinical, subject to the requirements of the Union authorities' legal acts and the Member State's legislation on clinical trials.

The refusal to agree upon shall include a detailed justification of the reasons for the non-conformity in any of the following cases:

where there is reason to believe that the study contributes to the marketing promotion of a medicinal product;

where the study plan does not allow the completion of the study objectives.

The study can be started only after written approval of the protocol by the Member State's authorised authority.

After the study starts, any significant changes to the protocol are submitted to the Member State's authorised authority before their introduction. The Member State's authorised authority within 60 calendar days after the submission of changes to the study plan shall assess these changes and inform the MA holder about their approval or rejection. Where the significant changes to the protocol are rejected, the written opinion of the Member State's

authorised authority shall include an indication of the time period for re-submitting changes to the study protocol.

The Member States' authorised authorities ensure the exchange of information on the results of the post-authorisation safety study protocols assessment regarding medicinal products that are authorised in the territories of other Member States.

Once the study is completed, the MA holder submits the final study report, including a summary of the study, to the Member State's authorised authority for publication. Based on the result of reviewing the report and assessing the possible impact of the data obtained on the risk–benefit ratio of the medicinal product, the Member State's authorised authority shall determine the need for submitting the recommendations on changing the authorisation status of the medicinal product, changing the conditions for its use, the need for applying other appropriate measures to ensure the product use when the benefit overweighs the risk. These measures to ensure the use of a medicinal product with a positive risk–benefit ratio shall be taken after the interim report's assessment if new important safety data of a medicinal product are identified at the interim data evaluation stage.

XI. Sharing Safety Data

1. Objectives of Safety Information Sharing

856. Safety information sharing helps build public confidence in the regulatory system, aiming at:

a) submission of timely, scientifically-based information on the safe and effective use of medicinal products;

b) assistance in the optimisation of medical practice (including the practice of self-medication), where necessary;

c) change in approaches, established practice, and the nature of the use of medicinal products;

d) support of activities related to risk minimisation;

e) assistance in making informed decisions on the rational use of medicinal products.

Safety Information Sharing Principles

857. The following safety information sharing principles should be applied:

a)the need to include in the safety information relevant, clear, reliable, and correct information for transmission to the target audience promptly to ensure the possibility of taking appropriate measures;

b) the need to adapt safety information using appropriate language tools and taking into account different levels of education and the need to obtain information from different target audiences (for patients and healthcare professionals), subject to retaining the accuracy and meaning of the information transmitted;

c) safety information sharing shall be part of the pharmacovigilance activity and risk management process, and is part of the risk assessment process and risk minimisation measures;

d) the need to ensure proper coordination of activities and interaction between the parties involved in creating and exchanging safety information (authorised authorities, other state authorities, and MA holders);

e) the need to provide information on the risks, considering the overall assessment of the benefits of a medicinal product, including available and up-to-date information on the seriousness of adverse reactions, severity, frequency of adverse reactions, risk factors for their development, time of

onset, reversibility of adverse reactions and, if possible, the expected recovery period;

f) safety information sharing shall help to resolve uncertainties in safety data. This is especially true in new information emerging when the Member States' authorised authorities carry out the safety data assessment procedures. The benefits of communicating at this stage shall be weighed against the risk of an error that could arise if the profile's uncertain aspects were not adequately explained.

g) the need to take into account competing risks (for example, the risk of refused treatment) (if any);

h) The need to use the most reasonable quantitative indicators when describing and comparing risks (e. g., indicators of relative risks and absolute risks). To compare risks, the patient groups shall be similar in their characteristics. Other ways of presenting information can also be used (graphical presentation of risk assessment and/or the risk–benefit ratio);

i) the need for prior consultation with healthcare professionals or patients when preparing safety information (when preparing information on complex safety concerns);

j) safety information sharing shall include the submission of follow-up information (e. g., supposed changes to recommendations, resolution of the safety concern) (where necessary);

k) assessing the efficacy of safety information sharing (where necessary and possible);

l) compliance of safety information with the requirements for personal data protection.

2. Target Audiences

858. The main target audiences for safety information sharing by the authorised authorities and MA holders are healthcare professionals, patients, and caregivers who use medicinal products (prescribe, dispense, participate in turnover, administer or take).

859. Healthcare professionals play a key role in the primary target audience. Effective communication on the safety of drugs allows them to conduct pharmacotherapy, considering the most relevant safety information and recommendations and providing understandable and useful information to patients, contributing to patients' safety and increasing their confidence in the regulatory and the healthcare system.

860. Patients, consumers, and healthcare professionals can play an important role in disseminating the important safety information among relevant target audiences.

861. The media is also the target audience for safety information. The media's ability to reach patients, healthcare professionals, and the general public is an important factor in distributing new and important information about a medicinal product. Disseminating the said information through the media impacts public opinion shaping; therefore, the media need to receive safety information directly from the authorised authorities and the information they receive from other sources (e. g., from the MA holders).

3. Safety Information Content

862. The information disseminated in the course of the safety information sharing shall be objective and shall not be misleading.

863. Subject to the principles set out in subparagraph 857 of these Rules, safety information shall contain:

a) new important information about any authorised medicinal product that affects the risk–benefit ratio of a medicinal product under any conditions of use;

b) reasons for initiating the safety information sharing procedure in a form understandable to the target audience;

c) necessary recommendations to healthcare professionals and patients related to the safety concern being informed;

d) indication of the agreement between the MA holder and the Member State's authorised authority on the provision of safety information (where applicable);

e) information about all proposed changes in information about a medicinal product (e. g., in the summary of product characteristics or package insert);

f) additional information on the use of a medicinal product or other necessary data to make the report available to the target audience;

g) bibliography or references to sources, containing more detailed information about a specific safety aspect identified in the safety information;

h) reminder to report suspected adverse reactions to the Member State's authorised authority through the national spontaneous reporting system of the Member State.

864. Safety information must not be misleading and shall be presented objectively. Safety information shall not contain advertising elements and other materials aimed at promoting the medicinal product.

4. Safety Information Sharing Means

865. When sharing safety information, it is necessary to use the full range of various media to reach target audiences and meet their growing

needs. Various means and channels of communication to be used are indicated in paragraphs 866–896 of these Rules.

Direct Address to Healthcare Professionals

866. Direct contact with healthcare professionals in these Rules means the submission by MA holders or the Member States' authorised authorities of important safety information directly to healthcare professionals to inform them about the need to take certain actions or change their practices of using the medicinal product following the new safety data.

867. Speaking directly to healthcare professionals is not an answer to healthcare professionals' questions.

868. The development of information material for direct submission involves cooperation between a MA holder and the Member State's authorised authority.

869. The MA holder shall obtain the approval of the Member State's relevant authorised authority in terms of the content of the information for direct contact with the healthcare professionals and the communication plan.

870. The procedure for agreement between the Member State and the MA holder's authorised authority shall be completed before distributing information materials by the MA holder.

871. Approval from the Member State's authorised authority shall be obtained concerning the content of the information and the communication plan, including the target audience, the schedule for distributing information, and means of its dissemination.

872. The Member State's authorised authority shall provide at least 2 working days for the MA holder to send comments on the remarks from the Member State's authorised authority regarding the information content or the plan of informing.

873. Where necessary, at the discretion of the Member State's authorised body a period other than that specified in paragraph 872 of these Rules may be established for this procedure due to the urgency of the situation that has arisen.

874. If there are several MA holders for the same active ingredient, for which it is necessary to provide information for direct address to healthcare professionals, the report shall be uniform and consistent.

875. When preparing information for direct address to healthcare professionals, consideration should be given to involving, where appropriate, the healthcare professionals or representatives of scientific societies to ensure that the information they provide is useful and relevant to the target audience.

876. The dissemination of a direct appeal to healthcare professionals shall be accompanied by the use of additional tools and channels for disseminating information.

877. Direct communication with healthcare professionals shall be included in the risk management plan as an additional measure to minimize risks.

878. Information for direct address to healthcare professionals shall be disseminated when urgent action is required. A change in existing practice concerning a medicinal product is required in the following cases:

a) suspension or cancellation of marketing authorisation due to changes in a medicinal product's safety profile;

b) making changes in the recommendations for using a medicinal product due to a limitation of indications, a new contraindication, or a change in recommended doses due to a change in a medicinal product's safety profile;

c) restrictions in the medicinal product availability in the pharmaceutical market or discontinuation of medicinal product manufacturing may adversely affect the healthcare delivery system.

879. Situations in which the need for direct address to healthcare professionals shall be considered:

a) new precautions or special instructions appeared in the recommendations for use of a medicinal product;

b) new data on the identification of previously unknown risk and changes in the frequency or severity of a known risk;

c) justified data appeared on the lower efficacy of the medicinal product;

d) new recommendations for preventing the adverse reaction development, or stopping adverse reactions or medicinal product abuse, and reducing the risk of medication errors;

e) information based on the results of a continuous assessment of important potential risks, where the data available on such risks at a certain point in time is insufficient for taking regulatory measures (in this case, direct address shall facilitate a close safety concern monitoring in clinical practice, reporting of adverse reactions, and informing about measures to minimize the potential risk).

The Member State’s authorised authority has the right to disseminate information for direct address to healthcare professionals or to request a MA holder to prepare, agree and disseminate information for direct address to healthcare professionals where the Member State’s authorised authority considers it necessary for further safe and effective use of a medicinal product.

880. authorised authorities of the Member States have the right to publish the final version of the information material for direct address to

healthcare professionals. Member State's authorised authorities may also issue additional safety reports (if necessary) and disseminate information to relevant organisations and healthcare professionals. Additional safety report is usually triggered when urgent action or a change in medical practice is required. It includes recommendations from the authorised authority and risk minimisation measures for healthcare professionals. Where a decision is made on the need for additional safety information sharing, the Member States' authorised authorities take into account the interests of the healthcare system and the population. To ensure the maximum dissemination of these additional reports, the Member States' authorised authorities shall select the most effective and targeted information channels. Where required, the outreach program may include the involvement of scientific and professional associations, patient organisations, local healthcare authorities.

Information for Non-Professionals in Healthcare

881. Information material written in an accessible language (e. g., in a question-and-answer format) helps persons who are not professionals in healthcare (patients and the public) (hereinafter referred to as non-professionals) understand the scientific issues and regulatory measures related to safety concerns.

882. Materials in layman's terms prepared by the MA holder shall contain recommendations and information from the Member State's authorised authorities on how to minimize risks arising from safety concerns to patients and healthcare professionals. They shall be accompanied by appropriate background information.

883. The Member States' authorised authorities post information for non-professionals on Member State medical Internet portals. They may further disseminate it among the patients and healthcare organisations, or use

other means and channels of information that provide the required level of dissemination and access to important safety information to the target audience.

884. Patients and healthcare professionals should be involved in the process of preparing documents in the terms understandable to the public in order to increase the availability of information.

Information in the Press

885. Information in the press include press releases and press conferences intended for journalists.

886. Authorised authorities of the Member States may send press releases directly to journalists in addition to posts on the websites of the Member States' authorised authorities, which will allow journalists to directly obtain information assessed by the Member State's authorised authority. Engaging with the media is an important way to reach a wider audience and build trust in the regulatory system.

887. MA holders may prepare and publish a press release to present their position on a safety concern, indicating the regulatory actions taken by the authorised authority.

888. As far as press releases can be read (besides journalists) by other readers (e. g., healthcare professionals, patients, and other non-professionals), they should contain reference to information materials relevant to the safety concern in question. Where a direct address to healthcare professionals is being planned, they should be informed, either before or at the same time the press release is published or disseminated, to enable healthcare professionals to be prepared to respond to patients' questions.

889. Where a safety issue is of heightened interest to the media or if there is a need to convey multifaceted and complex information on an

important public health issue to the public, the Member States' authorised authorities may consider holding a press conference with journalists as an effective method of informing the public.

Website

890. The website is an important information-sharing tool for the public (including patients and healthcare professionals). The Member States' authorised authorities and MA holders shall ensure that important safety information posted on the websites they control is easily accessible and understandable to users. The information on the sites shall be constantly updated, and any outdated information shall be marked accordingly or removed.

Other Means of Internet Communication

891. Safety information may also be disseminated on the Internet through other web applications. When using newer, high-speed communication channels, you should take the necessary measures to ensure that the transmitted information's accuracy is not compromised. Communication practice should take into account the emerging new means of communication used by various target audiences.

Informational Letters and Bulletins

892. Informational letters and bulletins are designed to regularly provide new information about medicines and their safety and efficacy. Through these information-sharing mechanisms, the Member States' authorised authorities can reach a large audience using web applications and other available means.

Interaction Between the Member States' authorised authorities

893. When one of the Member States' authorised authorities takes regulatory measures concerning a certain safety concern, other the Member States' authorised authorities may need to respond to inquiries or exchange information. It is recommended to use inter-regulatory information materials prepared by a Member State's authorised authority to help their colleagues respond to external inquiries or exchange information on a specific safety concern.

Answers to Public Requests

894. The Member States' authorised authorities and MA holders shall have functioning systems for responding to inquiries from the population about medicinal products. The responses shall contain publicly available information and include appropriate advice for patients and healthcare professionals provided by the Member States' authorised authorities. Where patients ask for advice on personalised treatment, they should be advised to consult a healthcare professional.

Other Means of Transmitting Information

895. Besides the means of informing specified in paragraphs 866–894 of these Rules, there are other tools and channels for transmitting information on safety (e. g., publications in scientific journals and journals of professional organisations).

896. Some tools and communication means can be used in risk management. Risk minimisation measures often include specialised risk information-sharing programs. The tools used in these programs (e. g.,

patient alert cards, educational materials, or safety guides for healthcare professionals) are specified in Section XII of these Rules.

5. Effectiveness of Safety Information Sharing

897. Safety information sharing is considered effective if the transmitted report is accepted and understood by the target audience in the way it was intended. The target audience responds to the information by taking appropriate measures. Appropriate mechanisms based on clear parameters (indicators) shall be used to assess the effectiveness of information sharing. Indicators can be based on the measurement of various outcomes, including, for example, behavior, relationships, knowledge, and other parameters or factors that characterize the effectiveness of information-sharing activities. Based on the effectiveness assessment, conclusions shall be drawn, priorities identified for further information-sharing activities, and tools and practices shall be adapted to meet the target audience's needs (where necessary). To establish the safety information's conformity with the requirements of paragraph 857 of these Rules, an approach based on target audience study should be applied. By applying this approach, various results of target audience assessment can be compared, including behavior, relationships, and knowledge.

898. MA holders are responsible for assessing the effectiveness of direct sharing of safety concern information with healthcare professionals. MA holders shall inform the Member States' authorised authorities about the number of healthcare professionals who received information in the form of direct address to healthcare professionals, the results of the assessment of the effectiveness of the direct address, and difficulties detected (e. g., problems with the list of recipients or deadlines and dissemination mechanisms). Appropriate corrective and preventive actions shall be taken whenever

insufficient effectiveness in the direct address to healthcare professionals is detected.

6. Requirements for the Safety Information Sharing Quality System

899. Following the requirements for the safety information sharing quality system set out in Section 2 of these Rules, it is required that procedures are in place to ensure that safety information sharing complies with the principles provided by paragraph 857 of these Rules. Control procedures shall be implemented and documented concerning the transmitted safety information that is the quality control object.

7. Interaction in Safety Information Sharing in the Member States Territories

Interaction of the Member States' authorised authorities in Sharing Information on Medicinal Products' Safety

900. Within the framework of information interaction between the Member States' authorised authorities, the authorised authorities carry out a regular exchange of information concerning the safety information planned for placement.

Direct Address to Healthcare Professionals on the Issues of Safety of Medicinal Products Authorised in the Member States Territories

901. If a medicinal product is authorised in the territory of one or more Member States, the Member States' authorised authorities share data on the approved content of the information for direct contact with healthcare professionals and the information plan that has passed the approval procedure. To exchange the final version of the information material and the information transfer plan, the Member States' authorised authorities use the available information exchange systems.

Requirements for MA Holders

902. The MA holder is obliged to inform the authorised authorities in the territory of which a medicinal product is authorised about his/her intention to make a public announcement, inform, or post information on pharmacovigilance, safety concerns, or issues related to the use of the appropriate medicinal product. Information aimed to inform and obtain approval shall be submitted to the authorised authorities, provided that it is prohibited from publication until at least 24 hours expire before its publication. Notifying the authorised authorities simultaneously with providing information to the public is possible only in exceptional cases, where there are grounds.

903. The grounds specified in paragraph 902 of these Rules include a reasonable threat to the life, health or well-being of the population.

904. The MA holder is responsible for the objectivity and accuracy of the information provided to the public. Where the MA holder receives information that a third party intends to disseminate information that may affect the risk–benefit ratio of a medicinal product authorised in the territories of the Member States, the MA holder shall inform the relevant Member States' authorised authorities.

Interaction with Third Parties

905. Third parties (scientific journals, scientific societies, patient organisations, etc.) should inform the Member States' authorised authorities about the emerging new safety information of medicinal products authorised within the Union. Where it is planned to publish this information, it is necessary to familiarize the Member States' authorised authorities with it before publication.

Selecting a Language and Performing Translation when Preparing a Direct Address to Healthcare Professionals

906. Important safety information disseminated through various information-sharing methods shall be communicated to the target audience promptly and in the official language of the Member State in which the relevant medicinal product is authorised.

907. When preparing and approving safety information intended for dissemination, the Member States' authorised authorities use Russian or another state language of the Member State.

908. Information of direct address to healthcare professionals is developed by the MA holder and submitted for approval to the authorised authority in Russian or another state language of the Member State. It is allowed to disseminate only the information approved by the Member State's authorised authority as a direct address to healthcare professionals in Russian or another official language of the Member State.

XII. Risk Minimisation Measures

1. General Provisions

909. Risk minimisation measures are actions aimed at preventing the development of adverse reactions, reducing the frequency or severity of adverse reactions, and minimizing the adverse consequences of exposure to a patient when an adverse drug reaction develops.

910. The risk minimisation measures included in this section are considered in accordance with the requirements for the risk minimisation system established by Section VI of these Rules.

911. Risk minimisation measures can include routine risk minimisation measures or additional risk minimisation measures. Routine risk

minimisation measures specified in Section VI of these Rules apply to all medicinal products.

912. Most safety concerns can be adequately managed with routine risk minimisation measures, additional risk management may be applied to some risks for which routine risk minimisation measures may not be sufficient to provide adequate risk management and/or better risk–benefit ratio of a medicinal product.

913. This section contains guidelines for applying additional risk minimisation measures, selecting the risk minimisation tools, and assessing the effectiveness of risk minimisation measures. In certain circumstances, an assessment of effectiveness may be required for routine measures to minimize the risk associated with safety concerns (e. g., where the summary of medicinal product characteristics includes recommendations for minimizing the risk that is not required by routine standards of medical practice). In these cases, recommendations for assessing the effectiveness of risk minimisation measures also apply to routine activities.

914. Risk minimisation measures are determined based on the safety concerns presented in the safety specification. Each safety concern should be considered on an individual basis; when choosing the most appropriate risk minimisation measure, it is necessary to consider the seriousness of potential adverse reactions, their severity, preventability, or clinical actions necessary to reduce the risk, indications, route and mode of administration, target populations, and the type of healthcare facility where the medicinal product is used.

915. More than 1 risk minimisation measure may be applied to manage a safety concern, and 1 risk minimisation measure may cover more than one safety issue.

916. The MA holder is responsible for ensuring proper control over implementing risk minimisation measures included in the risk management plan approved by the authorised authorities or specified as obligatory conditions for authorisation.

917. The authorised authorities are responsible for monitoring the results of the introduction and implementation of risk minimisation measures included in the risk management plan or specified as obligatory conditions for authorisation.

918. Risk minimisation measures aim to optimize the safe and effective use of a medicinal product throughout its entire life cycle. The risk–benefit ratio of a medicinal product can be improved by reducing the risk and severity of adverse reactions and optimizing the benefits through targeting and/or excluding patients or carefully monitoring treatment (specific regimen, laboratory monitoring, follow-up for patients, etc.). Risk minimisation measures shall guide the optimal use of the medicinal product in medical practice to ensure that the optimal product suitable for a patient at the optimal dose and with the optimal administration schedule is provided by a specialist who is properly trained in drug prescribing and patient management and with provision of reliable information and proper control.

919. Most safety concerns can be properly managed with routine risk minimisation measures. In certain cases, for certain important risks, routine risk minimisation measures may be assessed as insufficient, and additional risk minimisation measures are required for proper risk management.

When determining the need for additional risk minimisation measures, safety priorities are taken into account in terms of frequency, seriousness of adverse reactions, their severity, impact on the public health system, and risk avoidance. Next, an assessment is made of the possibility of achieving the set objective of minimizing risk when using routine measures and (where these

measures are assumed to be insufficient) additional minimisation measures are determined which most comply with the set objectives. Additional risk minimisation measures shall be applied to the most important and avoidable risks, while the burden on all parties involved in the implementation of these measures shall justify the expected benefit to patients.

920. There are several various methods used as complementary risk minimisation measures. The regulation sphere of the medicinal product circulation is under continuous development, and existing methods will be supplemented by new ones, including those focused on the wider use of information technologies.

921. The successful implementation of additional risk minimisation measures requires all stakeholders' involvement, including MA holders, patients, and healthcare professionals. It is necessary to assess how these measures are implemented in the healthcare system to ensure that the objectives are achieved and to determine the proportionality of the measures taken to the risk–benefit ratio of the medicinal product and the efforts required on the part of healthcare professionals and patients to implement such measures. An important condition for introducing additional risk minimisation measures, including an assessment of their effectiveness, is the exclusion of an excessive and unreasonable burden on the healthcare system, MA holders, authorised authorities, and patients.

922. Additional risk minimisation measures shall have a clearly defined objective consistent with the overall objective of minimizing specific risks and/or optimizing the risk–benefit ratio. Specific objectives and predetermined parameters for assessing the achievement of these objectives with key implementation stages shall guide the development of additional risk minimisation measures and assess the achieved target level of effectiveness.

923. Proper implementation monitoring and assessment of the effectiveness of additional risk minimisation measures against predetermined parameters should be ensured at the measures implementation stage during and after their completion.

924. To ensure the achievement of the desired results in the public health (health of population) protection when choosing tools or methods for minimizing risk and a strategy for implementing risk minimisation measures, the characteristics of the safety concern are taken into account in terms of:

risk–benefit ratio of the medicinal product;

the therapeutic value of the medicinal product;

target population;

necessary clinical actions aimed at risk minimisation.

Regular interim assessment of the effectiveness of the implemented risk minimisation measures shall be aimed at timely identification of their insufficient effectiveness, implementing the appropriate corrective measures and making changes to the plan of risk minimisation measures. This area is a growing sphere of medical sciences, which has no generally accepted standards and approaches, so it is permissible to apply appropriate approaches and quantitative methods used in pharmacoepidemiology or other branches of science (for example, in sociology or behavioral sciences), and qualitative research methods.

925. The introduction of additional risk minimisation measures should be seen as a program that develops specific methods, a plan of their implementation and an assessment strategy. The risk minimisation plan is an integral part of the risk management plan. The risk minimisation plan shall include the following sections:

a) justification: justification of the proposed additional risk minimisation measures, if it is required to introduce them;

b) objectives: specifying particular objectives and describing in detail how the proposed additional risk minimisation measure will address a particular safety concern for each of the proposed additional measures;

c) description: describing the additional risk minimisation measures selected, including a description of the tools or techniques that will be used and the key content elements;

d) implementation plan: a detailed description of proposals for the implementation of additional risk minimisation measures (e. g., characteristics of interventions, detailed information about the target audience, a plan for conducting educational programs and/or distributing educational tools, a mechanism for coordinating the measures with other MA holders, where necessary);

e) assessment plan: a detailed plan with key stages for assessing the effectiveness of additional risk minimisation measures in terms of the effectiveness of the planned process and determining overall indicators of impact on outcomes (e. g., risk reduction).

2. Additional Risk Minimisation Measures

926. Additional risk minimisation measures are proposed in cases where they are assessed as conditions for the safe and effective use of a medicinal product. The proposed additional risk minimisation measures shall be scientifically based, developed, and presented by appropriately qualified specialists.

927. Additional risk minimisation measures can vary in purpose, design, target audience, and complexity. These measures may be used to ensure the proper selection procedure for patients for whom the benefits of a medicinal product exceed the risks, and to exclude patients for whom the product is contraindicated, to ensure proper monitoring of therapy relevant to

the control of important risks and/or proper management of adverse reactions in the event of their development.

928. Additionally, specific risk minimisation measures can be developed concerning the risk of medication error and/or to ensure the proper prescription of a medicinal product in cases where it is impracticable to achieve this objective only by providing information about the product in the package insert or information on the label.

929. Where a request for additional risk minimisation measures is made, the request justification shall be documented, specific safety concerns shall be identified, and detailed planning of the implementation stages of risk minimisation measures and their assessment shall be provided.

930. Additional risk minimisation measures may include the following areas:

a) educational programs;

b) controlled access programs;

c) other risk minimisation measures.

3. Educational Program

931. Risk minimisation tools or methods used in an educational program are based on targeted information sharing that includes presentation of information in the summary of product characteristics or package insert. Any educational material should be oriented towards achieving particular objectives of risk minimisation.

932. The educational program objective is to optimize the use of a medicinal product by positively influencing the actions of healthcare professionals and patients to minimize the risk. Educational material development shall be based on the assumption that there is a practicable and actionable recommendation, which can be adopted by the target audience and

the application of this measure is an important and significant step to minimize risk and/or optimize the risk–benefit ratio.

933. Used in the context of an educational program, educational tools may have several various target audiences, may also be aimed at more than one safety concern and can be communicated using modern information and communication technologies (Internet), mass media, through the use of a combination of tools (on paper, audio, video conferencing) and through personal training. Provision should be made for presenting the materials in various formats to ensure access to these materials, including in the event of a malfunction of the informing tool or the impossibility of accessing the Internet. The educational tool used and the choice of media should be adapted to the needs of the target audience (e. g., the choice of language, type of images, diagrams or other graphical accompaniment of the educational tool). To optimize the results of the educational program implementation, preliminary testing of the educational tools used on the target audience should be provided.

934. The content of any educational materials shall be fully consistent with the information approved by authorised authorities for a medicinal product (summary of the medicinal product characteristics or the package insert). Educational materials can serve as a supplement to the information on the medicinal product approved by the authorised authorities. Educational materials shall not contain any advertising elements (direct or veiled (e. g., a logo, a characteristic color design of a product, stimulating images)) but shall include information on the risks arising from the medicinal product use and management of risks that require additional measures to minimize them.

935. The educational program shall be completely separate from the medicinal product advertising campaign. It is not allowed to use for

advertising purposes the doctors and patients' contact information obtained in course of educational programs.

936. The educational tools specified in paragraphs 937–942 of these Rules can be used individually or in combination when developing educational programs to further minimize the risk.

4. Educational Tools

937. Educational tools shall have a specific focus and include a definition of risk based on existing risks and specific actions to be taken by healthcare professionals and/or patients to minimize such risks.

938. Information in educational tools shall contain information about specific actions relevant to specific safety concerns in terms of risk minimisation, and shall not contain any information irrelevant to the safety concern. Information on educational materials shall include a reference to the summary of product characteristics or package insert.

939. Educational tools designed to ensure the safety and efficacy of a medicinal product and the appropriate management of important risks may include:

a) the procedure for prescribing the medicinal product, including patient selection, control and monitoring in order to minimize risks;

b) guidelines for managing the risks referred to in subparagraph "a" of this paragraph (for healthcare professionals, patients or carers);

c) guidelines for reporting identified adverse reactions of particular interest to characterize a risk.

Educational Tools or Methods Applied for Healthcare Professionals

940. The purpose of this educational tool for healthcare professionals is to provide risk-related recommendations for use and/or contraindications and/or warnings associated with the use of a medicinal product, as well as specific risks requiring additional risk minimisation measures, including:

a) patient selection;

b) treatment method, dosage regimen, control, and monitoring;

c) special administrative procedures or dispensing of a medicinal product;

d) detailed information to be presented to patients.

941. The choice of the format of the educational tool or method depends on the information presented. If a certain number of steps are required before a prescription for an individual patient is required, then a checklist may be an appropriate format. The brochure format may be more appropriate for professionals to be aware of specific risks for the purpose of early detection and management of adverse reactions. At the same time, posters may contain applicable therapeutic guidelines or drug regimens. The choice of the educational tool format depends on the focus, amount of information, target audience and other factors.

Educational Tools or Techniques for Patients and their Caregivers

942. Educational tools or methods applied to patients and individuals shall be aimed at improving the understanding of signs and symptoms at the stage of early detection of adverse reactions requiring additional risk minimisation measures and optimizing further patient management. Where necessary, an educational tool or method can be used to provide information and remind the patient of important actions (keeping records of medicinal

product dosing or diagnostic procedures to be recorded or performed by the patient, followed by a discussion with healthcare professionals to ensure compliance with any steps necessary for the effective use of a medicinal product, etc.).

Patient Alert Card

943. The purpose of this tool is to ensure that information on a patient's current treatment and treatment-related risks (e. g., potential interactions with other medicinal products) is always available to the patient and available to the healthcare professional. The information shall contain the minimum necessary to transfer key instructions to minimize risk and necessary actions to alleviate the condition under all circumstances, including emergencies. One of the key characteristics of this tool shall be portability to ensure ease of use.

5. Controlled Access Program

944. A controlled access program consists of a list of measures aimed at controlling access to a medicinal product beyond the level of control guaranteed by routine risk minimisation measures, i. e., the regulatory status of the product. Controlled access should be considered as a risk minimisation measure for a serious risk (e. g. risk of developing adverse reactions that pose a threat to life) for a medicinal product with proven benefit (e. g., medicinal products for treating a life-threatening condition for which there are no alternative therapies in the target population or subgroup of the target population due to the ineffectiveness of alternative therapies) that cannot be achieved without applying some additional risk minimisation measures.

945. The activities, which shall be completed before the medicinal product prescription and/or dispensing and/or use in the controlled access program, are performed individually or in combination with other activities. Such medicinal products shall include among others:

a) specific methods of control and/or examination of the patient to confirm the patient's compliance with certain clinical criteria for prescribing the medicinal product;

b) documentary confirmation by the doctor who prescribed the medicinal product, the pharmacist who dispensed the medicinal product, and/or the patient receiving and understanding information containing an explanation of the risk arising from the medicinal product use

c) using precise procedures for the patient's systematic follow-up through registration of information about such patient in a special data collection system (in the patient register), etc.

d) dispensing (sale) of medicinal products only through pharmacies that have a special permit (license) for dispensing (sale) of such medicinal products.

946. In certain cases, as a tool for controlled access, special methods of examination or monitoring of the patient's condition are carried out (e. g., monitoring the patient's condition, laboratory parameters or other types of research (ECG, etc.) before treatment and/or during treatment, liver function tests, regular blood tests, pregnancy test (which may be part of a pregnancy prevention program)). The said measures are introduced to ensure control following the summary of product characteristics where this is a critical factor in terms of the risk–benefit ratio of the medicinal product.

6. Other Risk Minimisation Measures

Controlled Medicinal Product Distribution System

947. A controlled distribution system refers to the types of measures intended to ensure that all stages of medicinal product transporting are tracked to the place of prescribing and/or dispensing a medicinal product by pharmacies. Ordering and shipping a medicinal product by one or more identified distributors facilitate the traceability of the product. For example, these measures may be considered for those medicinal products which are controlled in each Member State under its own legislation in order to prevent misuse and abuse of medicinal products.

Pregnancy Prevention Program

948. A pregnancy prevention program is a set of measures to minimize the risk of exposure to a drug with a known or potential teratogenic effect on the fetus during pregnancy. This program shall ensure that female patients have a control mechanism in place to ensure that the medicinal product is not prescribed during pregnancy and pregnancy does not occur during the treatment and/or a certain period of time after therapy cessation. A pregnancy prevention program may also target male patients if the biological father’s use of the drug could have negative consequences for the pregnancy outcome.

949. A pregnancy prevention program includes educational tools and appropriate tools to control access to the medicinal product. When planning a pregnancy prevention program, the following elements should be considered (both individually and collectively):

a) educational tools aimed at healthcare professionals and patients to inform about teratogenic risk and the necessary actions to minimize this risk

(guidance on the use of more than one method of contraception and guidance on using various types of contraceptives, information for the patient on the length of the period, during which pregnancy should be avoided after stopping treatment, etc.);

b) controlled access at the stage of prescribing or dispensing of a medicinal product to ensure the performance of a pregnancy test and monitor negative results by a medical professional and pharmacist before prescribing or dispensing the product;

c) limiting the maximum validity of a prescription (30 calendar days);

d) counseling in the event of unplanned pregnancy and assessing the outcome of an accidental pregnancy.

950. Consideration should also be given to the feasibility of developing and introducing a pregnancy register to record data for all patients who become pregnant during treatment or during an appropriate period of time since the end of treatment (e. g., during 3 months). Using a tool for systemic collection of information on pregnancy cases and outcomes contributes to collecting information on the effectiveness of the ongoing pregnancy prevention program and collecting information on risk characteristics, especially at the initial post-authorisation stage (i. e., at the stage when there are significant limitations or lack of data on pregnancy outcomes).

Direct Address to Healthcare Professionals

951. Direct address to healthcare professionals specified in paragraph 866 of these Rules is needed to minimize certain risks and/or reduce the severity of adverse drug reactions specified in Section XI of these Rules.

7. Implementing Risk Minimisation Measures

952. Additional risk minimisation measures may include the application of one or more measures that shall be implemented and performed for a specific target audience. Adequate attention shall be paid to both the timing and frequency of implementation of risk minimisation measures and procedures to achieve the objectives in the target audience. For example, one-time dissemination of educational tools may not be sufficient to ensure that all healthcare professionals potentially prescribing the medicinal product and/or consumers are informed, including new healthcare professionals and consumers. There may be a need for additional dissemination of educational tools or program methods to implement risk minimisation measures. Due consideration shall be given to the overall format of educational tools or programs to ensure a clear distinction from promotional material. Since risk minimisation measures are aimed at different purposes, some of these measures (e. g., patient alert cards, controlled access programs, and pregnancy prevention programs) shall, in most cases, support further medicinal product administration, while others (e. g., direct information sharing with healthcare professionals and educational materials) may not be required in subsequent drug administration stages. Feasibility of selecting each risk minimisation measure and the need for its implementation at the subsequent stages of the medicinal product use shall be considered, evaluated, and reflected in the risk management plan at the stage of subsequent submission for the product authorisation. The submission of educational materials for approval to the Member State’s authorised authority shall be carried out separately from the dissemination of advertising material. At the same time, the cover letter shall indicate whether the materials are advertising or educational. Educational materials should be distributed

separately from promotional materials, with an indication that they are not promotional. Quality assurance mechanisms shall ensure that the distribution systems in place are adequate for the intended purpose of the risk minimisation measure and are controlled and audited.

8. Assessing the Effectiveness of Risk Minimisation Measures

953. Assessing the effectiveness of risk minimisation measures is necessary to establish the effectiveness of risk minimisation measures application, identifying the causes of ineffectiveness, and the need for corrective action. The effectiveness of measures is assessed for each measure of risk minimisation and the risk minimisation program as a whole.

954. The time frame for assessing the risk minimisation measures shall be carefully planned as part of the risk management plan before initiating measures, taking into account the time required to commence implementation of the risk minimisation measures, the amount of drug use by the healthcare system, and other factors that affect the timing of planned activities.

955. Plans should be developed to periodically review the effectiveness of one or more of the tools or the risk minimisation program as a whole. The following control points of effectiveness assessment are applied, which are of particular importance in assessing the specified program’s effectiveness:

a) after the start of implementing the risk minimisation program (e. g., within 12–18 months) to ensure the possibility of making changes to the risk minimisation program where necessary;

b) at the stage of assessing the confirmation of a medicinal product authorisation.

956. Assessing the effectiveness of risk minimisation measures at all implementation stages also includes determining the need to further apply the assessed additional risk minimisation measure.

957. Assessment of the risk minimisation measures effectiveness shall consider various aspects of the risk minimisation measure being implemented: the process (i. e. the extent to which the planned program has been implemented), its impact on the target audience's awareness of changes in the behavior of this target audience, and the result (how far the risk minimisation goals have been achieved). The design of the assessment strategy identifies aspects of the process of the risk minimisation plan implementation (hereinafter referred to as the process) and results that can be correctly measured to avoid inaccurate or misleading data or unduly burdening the healthcare system or other parties involved in the process of risk minimisation measure implementation. The timing of assessing each component of the proactive measure being implemented, and establishing the correct metrics against which to assess the effectiveness of the risk minimisation tool, shall be carefully considered by the MA holder and planned before initiating risk minimisation measures.

958. To assess the effectiveness of risk minimisation measures, 2 groups of indicators should be used:

a) process indicators;

b) results indicators.

959. Process indicators are necessary to establish positive dynamics in all stages of risk minimisation measure implementation. This group shall assess the degree of implementation of the planned program and the achievement of the required impact on the behavior or actions of the target audience. Program performance indicators shall be predetermined and monitored throughout the program. The data and experience obtained can be used to optimize corrective actions, if necessary. A process execution assessment can also improve understanding of the processes and causal

mechanisms by which additional risk minimisation measures have or have not achieved the desired control of specific risks.

960. Outcome indicators provide an overall assessment of the degree of risk control achieved by implementing risk minimisation measures. For example, if the aim of taking an operational measure is to reduce the frequency and/or severity of adverse reactions, the ultimate criterion of result assessment will be tied to that objective.

961. Where there is a justified impossibility to assess the result indicators (e. g., unreasonably large number of patients at risk, very rare adverse events), it is acceptable to base the assessment of the risk minimisation measures effectiveness on a reliable interpretation of process indicators.

962. Based on the procedure results for assessing the effectiveness of risk minimisation measures, a conclusion is made about the possibility of further implementation of the risk minimisation measure without changes or the need to change it. Assessment of the effectiveness of risk minimisation measures may indicate that risk minimisation activities are insufficient and shall be strengthened (through changes to precautions or recommendations in the summary of product characteristics and package inserts), improving the clarity of recommendations for minimizing risk and/or connecting additional tools to minimize risk or improve existing ones, etc.). Another result of the assessment procedure may be the identification of inconsistency of risk minimisation measures or the absence of the required focus in the assessment procedure, in connection with which the volume of work on the program may be reduced or its simplification may be considered (a decrease in the number of tools, or methods of risk minimisation, or the frequency of implementation of certain measures for risk minimisation, or exclusion of a part of the

implemented measures, for which it has been demonstrated that they do not make a significant contribution to risk minimisation).

963. In addition to assessing the effectiveness of risk minimisation measures in managing safety concerns, it is also important to assess whether an additional risk minimisation measure may have unintended (negative) consequences for the public health problem under consideration in the near or distant time frame. Examples of unintended consequences include unnecessarily overloading the healthcare system, stopping the use of a medicinal product by patients, including in cases of a positive risk–benefit ratio for these patients.

964. Studies assessing the effectiveness of risk management measures are post-authorisation safety studies. Thus, when conducting a study to assess behavior or safety indicators, the requirements for post-authorisation safety studies defined in Section X of these Rules shall be met. This guidance does not apply to the measurement of simple process indicators (e. g., dissemination of the information tools, containing risk minimisation measures in the target population). Where appropriate, methodological standards for assessing studies in pharmacoepidemiology may be used.

Assessing the Process Indicators

965. Process indicators are based on parameters for assessing the volume of implementation of the original program and/or changes in the process of its implementation. Process indicators shall complement, not replace, the assessment of achievement of intended objectives by implementing risk minimisation measures (result indicators). Depending on the nature of the active measures, various process indicators can be defined to assess their effectiveness.

Reaching the Target Population

966. When risk minimisation measures mean providing information and guidelines for healthcare professionals and/or patients by providing educational tools, dissemination assessment measures are used to obtain baseline effectiveness data. These indicators shall focus on assessing the delivery of the tool used to the target population and assessing the actual receipt of the materials by the target population.

Clinical Knowledge Assessment

967. To assess the target population's awareness and the level of knowledge gained through applying educational tools and/or using other methods of information delivery, scientific survey methods are applied.

968. The survey usually includes basic standard questions, the answers to which can be provided by telephone, in a personal interview, or sent by e-mail. Analytical surveys should be carried out regularly.

969. The approach specified in paragraph 968 of this Regulation can be adapted to monitor the attitude towards the proposed measures and the degree of awareness of representative groups of the target audience of healthcare professionals and/or patients and be carried out using appropriate psychometric tools. Adequate sample size should be determined for the above indicators assessment to be included using principles of randomisation. The use of initiative groups or patient support groups to conduct an analytical knowledge survey should not be used due to the biased principle of self-selection.

970. Due consideration should be given to the objectives of the survey, study design, sample size and representativeness of sample, operational definitions of dependent and independent variables, and statistical analysis.

Careful attention shall also be paid to selecting the most appropriate data collection tools (questionnaires, feedback forms, etc.).

Assessing the Clinical Actions

971. To assess the effectiveness of educational additional measures and/or information support, it is necessary to determine clinical knowledge and clinical actions based on it (e. g., prescribing a medicinal product).

972. Studies on using a medicinal product through the secondary use of data from electronic health records should be considered a valuable tool for quantifying clinical action if the appropriate number of participants, target audience and database are provided.

973. Analysis of prescription sheets subject to other patient's data (clinical, demographic data, etc.), can provide an assessment of prescribing of medicinal products, including concomitant prescribing two interacting products, compliance with laboratory monitoring recommendations, and patient selection and monitoring.

974. Applying statistical methods (time series analysis, survival analyses, logistic regression, etc.) for a cohort of drug users, it is possible to assess various aspects of prescribing or use medicinal products, allowing a prediction of risk minimisation goes beyond just describing the evidence. Particular attention shall be paid to the conduct and interpretation of the results of studies assessing the use of medicinal products in the Member States, including the authorisation status of a product and the procedure for its prescription and dispensing, since the procedure for prescribing a product may reflect not only information about the product and any measure to minimize the risk but also Member State's prescribing guidelines, health system aspects, practical use of the medicinal product and limits on treatment reimbursement. This diversity of healthcare delivery systems within and

outside the Member States may warrant study with the same objectives in several countries.

975. In the absence of previous data, the clinical action assessment shall account for the behavioral studies based on data collected from analytic interviews.

Assessing the result indicators

976. The indicators of the success of the risk minimisation program implementation are the results of increased safety of drug use (frequency and/or severity of adverse reactions due to drug exposure to the patient outside the intervention study).

977. An assessment based on indicators of the success of the risk minimisation program implementation shall include a comparison of epidemiological measures of outcome frequency, such as a measure of the frequency or cumulative frequency of adverse reactions obtained in the context of post-authorisation safety studies. Consideration should be given to using appropriate results of improving the medicinal product safety (e. g., a surrogate endpoint of the study (e. g., an appropriate biomarker, as a substitute for the clinical endpoint)) if such an approach facilitates the effectiveness assessment of the risk minimisation measures being implemented.

978. Under any approach, the scientific and recognised epidemiological study principles shall always guide the assessment of the final result indicator being used.

979. Consideration should be given to the comparison of frequency before and after the implementation of risk minimisation measures. Where it is impossible to perform a pre- and post-intervention assessment and calculation (e. g., risk minimisation measures were put in place at the time of

marketing authorisation), the outcome rate obtained at the post-intervention stage is correlated with a predetermined reference value obtained from the scientific, retrospective data from patient medical records, expected frequency in the general population (observed vs. expected analysis, etc.), and must consider the possible effect of incentives for reporting, changes in patient care, and/or measures to minimize risk. The selection of the comparison group shall be properly justified.

980. Methods for assessing the effectiveness of risk minimisation measures shall be comparable with the risks being minimised. The use of the indicator of spontaneous reporting (the number of reports of suspected adverse reactions in an established period of time) is acceptable in assessing the effectiveness of routine risk minimisation measures. Spontaneous reporting should be considered with caution when assessing the incidence of adverse reactions in the target population except in special circumstances (e. g., the incidence of an adverse event with a medicinal product is rare, the baseline incidence in the general population is low, and there is a marked relationship between the treatment and the adverse reaction).

981. In such circumstances, where a direct determination of the degree of risk in the group in question is impracticable, spontaneous reports might allow an assessment to be made of the approximate frequency of adverse reactions in the group, provided that some reasonable data can be obtained to assess the rate of repetition in the context of drug use.

982. The inherent uncertainties that affect the level of reporting of suspected adverse reactions can lead to misleading results. For example, introducing a risk minimisation program related to a safety concern identified during the post-authorisation monitoring phase of a medicinal product can raise awareness of certain adverse reactions, which may ultimately lead to an increased reporting rate.

983. In such circumstances, spontaneous reporting analysis may lead to the erroneous conclusion that the intervention was ineffective. Reduced reporting rates over a given time frame can also lead to the misconception that the intervention was effective.

9. Coordination

984. Where there is more than one medicinal product with the same active ingredient on the market, a unified approach is applied in relation to additional risk minimisation measures provided for by the Member States' authorised authorities. When there is a need for coordinating actions for a group of medicinal products, the Member States' authorised authorities should develop a coordinated approach. In such circumstances, advance planning shall ensure that the effectiveness of risk minimisation measures is assessed for each individual medicinal product, as well as for medicinal products in combination.

10. Quality Systems of Risk Minimisation Measures

985. Although many experts are involved in developing and implementing the risk minimisation measures, the responsibility for the quality, accuracy, and scientific integrity of such measures rests with the MA holder and the MA holder's authorised pharmacovigilance officer.

986. The MA holder is responsible for updating the risk management plan in the event of new information, the compliance of the information in the materials on risk minimisation measures with the summary of product characteristics and the package inserts, and shall also apply the quality principles specified in Section II of these Rules. Traceable versions of the risk management plan shall be submitted for review and assessment by the

Member States' authorised authorities. These documents, the risk management plan, and the risk management systems included in the plan and any other documents containing risk minimisation measures may be audited or inspected.

987. The MA holder shall ensure that mechanisms for reporting the results of studies or analyses to assess the effectiveness of risk minimisation measures are documented. These documents can be audited or inspected.

Responsibility of the authorised authorities of the Member States

988. The Member States' authorised authorities are responsible for implementing additional risk minimisation measures applied as a condition for the safe and effective use of a medicinal product. Additional risk minimisation measures established for medicinal products during authorisation under a decentralised procedure or mutual recognition procedure are included in the risk management plan and are conditions for authorisation. The introduction of additional risk minimisation measures at the Member State level can consider the legislation of the Member States and the characteristics of the health system, for example, measures to address certain risks can be implemented using different approaches, considering the capabilities of healthcare systems at the Member States level.

989. Concerning risk minimisation measures that were introduced after getting the marketing authorisation, the Member States' authorised authorities must ensure that they are promptly reviewed and agreed with the MA holder.

990. The Member States' authorised authorities, if necessary, can assist in the harmonisation of the risk minimisation measures introduced by the MA holders for generic medicinal products (generics) with the same active ingredient. If it is necessary to introduce additional risk minimisation measures for generic medicinal products and biosimilars due to problems

related to the safety of the active ingredient, the risk minimisation measures applied to the generic products and biosimilars should be brought in line with the risk minimisation measures for the reference product. Under certain circumstances, additional risk minimisation measures may be required for hybrid medicinal products and the risk minimisation measures introduced for the reference product (e. g., due to differences in formulation, route of administration, or incompatibility problems). An authorised authority of a Member State can help select the key risk minimisation tools to be implemented by MA holders and shall provide access to these recommendations by posting on a web portal to ensure harmonised implementation of risk minimisation measures at the Member State level.

991. The authorised authorities of the Member States shall ensure that any tool or method is used to minimize the risk. The authorised authorities of the Member States must agree with the applicant or the MA holder the format and means of tools or methods for minimizing risk, including printed materials, Internet platforms, and other audiovisual media, as well as planning (scheduling) of operational measures before the release of a medicinal product on their market or at other times (if necessary).

992. The Member State’s authorised authority makes a decision regarding selecting appropriate educational materials and other tools or methods to minimize risk; at the same time, it is recommended that authorised authorities of the Member States coordinate the key elements of the risk management plan. Implementing the measures to assess the effectiveness of additional risk minimisation measures may be required in the territory of one of the Member States due to the peculiarities of the conditions for the providing medical care in the Member State or the impossibility of applying the results of effectiveness assessment studies conducted in another Member State or a third country in relation to a program that includes risk

minimisation measures carried out in that Member State. The Member States' authorised authorities monitor the results of the risk minimisation measures introduction in the territory of this Member State.

993. Where the patient alert card is included in the secondary (commercial) packaging, it is considered part of the official information about the medicinal product and is subject to approval by the Member State's authorised authority.

12. Responsibility of the MA Holders

994. MA holders are responsible for compliance with the conditions for authorisation of medicinal products, including compliance with all conditions or restrictions regarding the safe use of the product in a certain territory.

995. The registrant must define the objectives of the proposed additional risk minimisation measures and the indicators for assessing their effectiveness. In case of a foreseeable need to adapt risk minimisation measures to the different conditions of healthcare systems operating in Member States, the MA holder should carry out preliminary coordination of risk minimisation plans with the Member States' authorised authorities as soon as possible. Any additional operational risk minimisation measures shall be developed in accordance with the general principles specified in paragraphs 918–951 of these Rules, and reflected in the risk minimisation program in accordance with Section VI of these Rules.

996. The measures approved by the Member State's authorised authority in the risk minimisation plan shall be implemented by the MA holder. The MA holder shall provide information on implementation of additional risk minimisation measures as agreed with the authorised authorities of the Member States, and inform the authorised authorities of the Member States about any changes, difficulties, or issues arising from the

implementation of additional risk minimisation measures. Any changes concerning the tools being implemented or methods for risk minimisation measures shall be agreed upon with the Member States' authorised authorities.

997. When introducing information technology-based tools or methods, MA holders shall apply the requirements specific to each Member State, considering potential problems of accessibility of risk minimisation measures, recognizability, MA holder's responsibility to introduce these measures, confidentiality, and data protection.

998. For generic products, the MA holder shall develop risk minimisation measures according to the volume, focus, content, and format of the instruments or methods used for the reference product. Scheduling and planning of operational measures shall be properly coordinated to minimize the burden on health systems.

999. Evaluation of the effectiveness of risk minimisation measures concerning generic products is carried out by the MA holder in cooperation with the Member States' authorised authorities. Where research is needed to minimize the burden on health systems, collaborative studies are required. For example, if a prospective cohort study is scheduled, study enrollment shall be independent of the prescription of a medicinal product with a specific brand name or from a specific manufacturer of the product. In these cases, the data registration for a particular medicinal product is important to quickly identify new risk inherent in a particular product.

1000. The MA holder should monitor the results of the risk minimisation measures that are included in the risk management plan. The general principles for assessing effectiveness are specified in paragraphs 953–983 of these Rules.

1001. The MA holder shall submit a report on the assessment of the effectiveness of additional risk minimisation measures related to the assessment of the risk–benefit ratio in the periodic safety update report.

1002. The MA holder shall ensure timely communication with the Member States' authorised authorities to carry out the appropriate regulatory assessment and actions in accordance with Section V of these Rules.

13. Healthcare Professionals and Patients

1003. Interaction of healthcare professionals and patients is a significant factor necessary for successfully implementing educational programs and /or controlled access programs to optimize the risk–benefit ratio. Special attention should be paid to any additional risk minimisation measures that may be introduced to ensure the safe and effective use of medicinal products.

14. Impact of the Risk Minimisation Measures Effectiveness on the RIsk Management Plan and Periodic Safety Update Report

1004. Updates to the periodic safety update report and risk management plan shall include a summary assessment of the result of additional risk minimisation measures introduced to reduce important risks associated with medicinal product use. The risk management plan should reflect the impact of the course of activities and their results on the planning of risk minimisation measures and/or pharmacovigilance. In a periodic safety update report, an assessment of the impact of the introduced measures on the safety profile and /or the risk–benefit ratio of the medicinal product shall be made. Special mention should be made of data obtained during the reporting period or since the implementation of recent risk minimisation measures.

1005. The results of assessing the risk minimisation measures effectiveness in all cases should be included in the risk management plan. As

part of this critical assessment, the MA holder should make observations about factors that contribute to achieving the objective or lead to inadequacy or ineffectiveness of risk minimisation measures. This critical analysis may include a reference to experience outside of the Member States (if any).

1006. Effectiveness assessment of risk minimisation measures shall reflect the degree of their effectiveness in relation to minimizing the target risk. Effectiveness assessment of risk minimisation measures is carried out for a combination of process indicators and result indicators in accordance with paragraphs 953–983 of these Rules. A distinction should be made between the risk minimisation measures introduced at the time of issuance of the marketing authorisation certificate and those measures that were introduced later at the post-authorisation stage.

1007. An assessment of the effectiveness of risk minimisation measures shall be presented considering the following recommendations:

a) The assessment shall contain the following items:

summary of the introduced risk minimisation measures;

their objectives defined;

descriptions of the selected process and result indicators;

b) the assessment shall include an analysis of the nature of adverse reactions, including severity and preventability of these reactions. Where necessary, logistical factors that may affect the clinical implementation of risk minimisation measures should also be considered;

c) the assessment shall include the implementation analysis of risk minimisation measures in routine clinical practice, including any deviations from the original plan. Such an assessment may include the results of studies on the use of the medicinal product.

d) result indicators shall be the key endpoints in assessing the degree of achievement of the assigned objectives in implementing risk minimisation measures.

1008. Proposals for making changes to the plan to improve risk management measures shall be presented in the appropriate section of the periodic safety update report. The risk minimisation plan should be updated based on received information about the risk minimisation measures' effectiveness.

1009. The frequency of updating the risk management plan shall be proportional to the risks associated with medicinal product use. The risk management plan update shall include an update of the risk minimisation program (where necessary).

1010. If changes are made to particular sections of the risk management plan, they shall be indicated in the cover letter when submitting the documents. Where, as a result of implementing the risk minimisation measures, it is required to make changes to the summary of the medicinal product characteristics, it is necessary to make changes to the information on the medicinal product. Based on the preparation of the periodic safety update report, the need to update the information on the medicinal product can also be determined.

15. Transparency in Introducing the Risk Minimisation Measures

1011. The Member States' authorised authorities ensure the transparency and availability of information on the introduced risk minimisation measures by posting the following information on the Internet portals: the current version of the summary of product characteristics, a summary of the risk management plan indicating the risk minimisation measures introduced.

1012. On the Internet portal of the Member States' medicinal products, the authorised authorities should provide free access to the following information:

a) a summary of product characteristics and a patient leaflet (package leaflet);

b) established conditions for the marketing authorisation, including the terms for fulfilling the conditions;

summary of the risk management plan, including the pharmacovigilance plan and risk minimisation measures;

c) information on additional risk minimisation measures required as a condition for the medicinal product authorisation (e. g., where risk-information sharing is implemented in the form of printed materials, a copy is provided, or electronic access to educational material is provided, a patient alert card, checklists or other tools (where possible)).

XIII. Additional Monitoring as part of the Good Pharmacovigilance Practice

1. General Provisions

1013. Pharmacovigilance is a necessary function of the healthcare system and aims to quickly identify and respond to potential safety threats associated with the use of a medicinal product.

1014. Authorisation of a medicinal product is carried out based on a positive risk–benefit ratio of a medicinal product for a specific target group of patients at the time of registration within the approved indications and recommendations for use.

1015. However, not all risks can be identified by the initial authorisation time; some risks are identified at the post-authorisation stage

with the widespread use of a medicinal product throughout the entire life cycle of the product.

1016. To ensure the possibility of monitoring the safety of medicinal products in proportion to the level of risk associated with their use, it is advisable to form a list of products requiring an expanded collection of safety data after their authorisation, which means the introduction of the concept of additional monitoring for some products.

1017. The Member States' authorised authorities create, update and publish on their official pages on the Internet a single list of medicinal products subject to additional monitoring (hereinafter referred to as the list) in the Member States territories. Such medicinal products in the general description of the product and package insert are indicated by an inverted black isosceles triangle (▼), which is accompanied by the following explanatory inscription: "This medicinal product is subject to additional monitoring. This will allow you to identify new safety information quickly. We are asking healthcare professionals to report any suspected adverse reactions."

2. Reasons for Medicinal Product Inclusion on the List of Medicinal Products Subject to Additional Monitoring

1018. Authorisation of all medicinal products is carried out based on recognizing the risk–benefit ratio as positive, considering the information available at the time of authorisation (data from clinical trials that were carried out during the product development). However, adverse reactions that rarely occur or develop with prolonged use may become apparent only after using a medicinal product by a wider range of patients and/or after long-term use. Besides, the benefits and risks associated with the use of a medicinal product may have been assessed in the settings different from general

medical practice; for example, clinical trials may exclude certain types of patients with multiple comorbidities or concomitant medications. Thus, after a drug is placed on the market, its use by different population groups requires constant monitoring. MA holders and authorised authorities constantly monitor the medicinal products to obtain emerging safety information and also assess its impact on the risk–benefit ratio of the product. However, some medicinal products require more intensive safety data collection after their state authorisation in order to quickly identify new significant safety concerns, and the immediately apply the appropriate measures. The concept of additional monitoring is used to improve the effectiveness of monitoring the safety of particular medicinal products and to encourage spontaneous reporting of identified adverse reactions.

1019. The status of additional monitoring can be assigned to a medicinal product while getting the marketing authorisation or at later stages of the life cycle of a medicinal product if a new safety concern is identified in the process of post-authorisation monitoring. In particular, the status of additional monitoring is important when issuing marketing authorisations for medicinal products containing a new active ingredient for all biological medicinal products, which are priorities for pharmacovigilance. The Member States' authorised authorities may also require to introduce additional monitoring status for a medicinal product under certain circumstances, such as the post-authorisation safety study results or restrictions on the safe and effective use of the product.

3. Data Sharing and Transparency in Additional Monitoring

1020. The additional monitoring status shall be communicated to healthcare professionals and patients so that the number of reports of suspected adverse reactions increases without creating an undue alarm. This

can be achieved, for example, by emphasizing the need to better characterize the safety profile of a new medicinal product by identifying additional risks but balancing these potential risks with the proven benefits and therapeutic benefits of the product. The Member State's authorised authority should constantly update the publicly available list of medicinal products with additional monitoring in terms of the circulation of medicines. Besides, healthcare professionals and patients shall be able to easily recognize these products by their labeling. Publishing the medicinal product list with explanatory information on the need for additional monitoring shall encourage healthcare professionals and patients to report all suspected adverse reactions that occur when using the medicinal products subject to additional monitoring.

4. Criteria for the Medicinal Product Inclusion in the Additional Monitoring List

Mandatory Inclusion Criteria

1021. The list of medicinal products subject to additional monitoring includes the following categories of medicinal products:

a) medicinal products authorised in the Member States territories containing a new active ingredient that, before the entry into force of these Rules, were not authorised in any Member States as part of any medicinal product;

b) biological medicinal products authorised a Member State territory after the entry into force of these Rules;

c) medicinal products for which the Member State's authorised authority requested a post-authorisation safety study at the time of issuance of the marketing authorisation or after issuance of the marketing authorisation.

Additional (Optional) Inclusion Criteria

1022. At the request of the Member State’s authorised authority, medicinal products can be included in the list of medicinal products subject to additional monitoring based on the following additional inclusion criteria:

Recommendations for using a medicinal product contain significant restrictions necessary to ensure its safe and effective use.

The Member State’s authorised authority has determined the use of other measures to ensure the safety of the medicinal product in the risk management system.

The Member State’s authorised authority has established an obligation for the MA holder to conduct a post-authorisation study of effectiveness.

The decision to include a medicinal product in the list of medicinal products subject to additional monitoring shall also consider the expediency of this status, considering the implementation of other additional pharmacovigilance activities proposed in the risk management plan.

5. Criteria for Determining the Additional Monitoring Period when Including in the List of Medicinal Products, Subject to Additional Monitoring

Mandatory Criteria of Correction

1023. For medicinal products containing new active ingredients and all biological products, the initial period of inclusion in the list of medicinal products subject to additional monitoring is 5 years from the date of authorisation in the Member State territory.

Additional Criteria of Correction

1024. For medicinal products included in the list based on the establishment of certain conditions (post-authorisation studies of safety,

efficacy, risk management system requirements), the period of inclusion in the list of medicinal products subject to additional monitoring is related to fulfilling relevant conditions and obligations imposed on the MA holder. The Member States' authorised authority determines it according to the completion rate and the results obtained.

1025. During the life cycle of a medicinal product, it may be repeatedly included in the list of medicinal products subject to additional monitoring.

6. Responsibilities of the Member States' Authorised Authorities

1026. The Member States' authorised authorities should:

a) provide information sharing with authorised authorities of other Member States about the decision taken to include authorised (approved) medicinal products in the list of medicinal products subject to additional monitoring, provide an electronic link to the web page of the Member State's authorised authority, where public access to information on the medicinal product and a summary of the risk management plan is open;

b) publish a list of medicinal products authorised in the Member States territories, which are subject to additional monitoring on websites on the Internet. The list contains an electronic link to the website of the authorised authority of the Member State on the Internet, where public access to information on the medicinal product and a summary of the risk management plan is open;

c) provide information sharing with authorised authorities of other Member States about medicinal products authorised in accordance with the Member States' legislation and included in the list of products subject to additional monitoring;

d) account for the list of medicinal products subject to additional monitoring when determining the frequency and features of the signal detection procedures;

e) provide information sharing with the MA holder about the decision to be included in the list of medicinal products for additional monitoring;

f) take all appropriate measures to ensure that healthcare professionals and patients report any suspected adverse reactions caused by using a medicinal product from the list of products subject to additional monitoring;

g) carry out a monthly update of the list of medicinal products for additional monitoring.

7. Responsibilities of the MA Holders

1027. The MA holder shall:

a) provide for including the symbol of a black isosceles triangle (▼) with accompanying information on the status of additional monitoring in the summary of the medicinal product characteristics and the package insert of the medicinal products included in the list of medicinal products subject to additional monitoring;

b) include information on the status of additional monitoring in material that will be distributed to healthcare professionals and patients and should stimulate the reporting of adverse reactions, as agreed with the Member States' authorised authorities;

c) provide the Member States' authorised authorities with information on the fulfillment of the conditions established by them;

d) submit changes to the summary of product characteristics and package insert for the inclusion or removal of the symbol of black triangle (▼) and accompanying information about the status of additional monitoring in the manner prescribed by the Rules for Marketing Authorisation and

Expert Assessment and the Requirements for package insert and summary of product characteristics approved by the Decision of the Council of the Eurasian Economic Commission No. 88 of November 3, 2016.

8. Using the black triangle symbol (▼)

1028. For the medicinal products included in the list of medicinal products subject to additional monitoring, the summary of product characteristics and package insert must contain the symbol of an inverted black isosceles triangle **(**▼), which is accompanied by the following explanatory note: “This medicinal product is subject to additional monitoring. This will allow you to identify new safety information quickly. We are asking healthcare professionals to report any suspected adverse reactions.”

1029. Once the medicinal product is included in the list of medicinal products subject to additional monitoring or removed from it, the MA holder is obliged to make appropriate changes to the summary of the medicinal product characteristics and package insert.

1030. Where the decision to include a medicinal product in the list of medicinal products subject to additional monitoring or removal from it is made during the procedure established by the legal acts of the Union authorities or the Member States’ legislation (authorisation or renewal procedures, changes to the summary of the medicinal product characteristics, etc.), it is necessary to make changes to the summary of the medicinal product characteristics and package insert before the procedure completion, in order to include or exclude the black triangle symbol from it with explanatory information.

1031. Where the decision to include a medicinal product in the list of medicinal products subject to additional monitoring or to remove it from this list is made regardless of the procedure established by the legal acts of the

Union authorities or the Member States' legislation, the MA holder is obliged, following the established procedure, to make appropriate changes to the summary of product characteristics and package insert."
