1. Definitions

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 missing information” is significant gaps in the available knowledge about certain aspects of the medicinal product's safety or groups of patients to whom the medicinal product is prescribed.

“Important identified risk” and “important potential risk” are the identified risks or potential risks that may have an impact on the risk-benefit ratio of the medicinal product or have consequences for public health. Determining a risk as important depends on several factors, including the degree of influence on the individual, the severity of the risk, and the impact on public health. As a rule, any risk considered in the contraindications and precautions section should be classified as an important risk.

“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 was 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.

“Signal detection” is the process of searching and (or) identifying signals using all signal 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. The end date of data collection includes the day and month.

“Risk minimization activity (measures)” is a set of measures aimed at preventing or reducing the likelihood of an adverse reaction associated with medicinal product exposure or at reducing the severity of an adverse reaction in the event of its development.

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

“Closed signal” is a signal whose assessment was 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.

For example: Adverse reactions reliably confirmed in preclinical studies and confirmed by clinical study data. Adverse reactions identified in well-designed clinical or epidemiological studies in which the degree of difference in the assessed parameter between the groups suggests a causal link. Adverse reactions predicted based on data from several spontaneous reports with an appropriate level of documentation; 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 are also identified risks, 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).

“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 authorized medicinal product, whether or not it is available, which may have a severe impact on public health.

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 drug, may also need to be considered emergencies. Likewise, other situations that may negatively affect the proper use of medicines (e.g., situations leading to medication discontinuation) may be relevant to an emergency.

An incident refers to a medicinal product authorized in the Union, regardless of the registration method.

“Solicited sources of individual case safety reports” are organized data collection systems that include clinical trials (studies), registries, post-marketing personalized 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 the 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 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 of the Eurasian Economic Union, 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 study.

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.

“Crisis” is a situation in which, after assessing the associated risks, it is required to take quick and coordinated actions within the Union legislation to manage and control the current situation.

“Drug (medicine)” 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 authorization holder concerning data on one or more authorized medicinal products.

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

“International Birth Date (IBD)” is the date of the first registration (authorization, approval for use) of a medicinal product containing a specific active ingredient in any country of the world.

If a marketing authorization 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 authorization holder should agree with the authorized authority on the possibility of using the first known date of
receipt of the marketing authorization for the active substance as the
international birth date.

“Risk minimization 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” is the minimum data for reporting
cases of suspected adverse reactions, including an identifiable reporter, an
identifiable patient, an adverse reaction, and a suspected medicinal product.

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

“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. Therefore, 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, medication
ersors.

“Adverse event” is any unfavorable change in the state of health of a
patient or study subject to whom a medicinal product was prescribed,
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 causal link with the drug use, regardless of the presence or absence
of a relationship with the product used.

“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 to routine clinical
practice, and the prescription of the medicinal product is separated from the
decision to enroll the patient in the study.

Patients undergo no additional diagnostic or control procedures, and
epidemiological methods are used to analyze the data obtained.

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, crossover, and
cohort studies). Non-interventional studies also include collecting primary data (particularly prospective non-interventional studies and registries that record the data obtained for a routine treatment process) when the above conditions are met.

In this context, interviewing, questioning, and blood sampling may be conducted as part of routine clinical practice.

“Misuse” is an intentional and inappropriate use of a medicinal product that does not comply with the current summary of product characteristics or package inserts.

“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, but is not limited to, 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 product characteristics or the Investigator's Brochure for an unauthorized medicinal product. Unexpected adverse reactions include pharmacological class effects indicated in the summary of product characteristics but have not been described as drug-related directly. For medicinal products authorized at the national level, the summary of product characteristics is applied, approved by the Member State's authorized 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.
“Company core data sheet” is a document developed by a marketing authorization holder, containing safety information, indications, dosage regimen, pharmacological properties, and other product-related information.

Company core safety information (CCSI) is information related to the safety of a medicinal product contained in the list of the marketing authorization holder's primary product data, developed by the holder and submitted, upon his request, to the authorized 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 authorized authorities. The marketing authorization 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.

“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.

“Medication error” is an unintentional error in the process of using a product that has led or could potentially harm a patient.

“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.

This process 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 Member State's authorized authority, after conducting the initial analysis and prioritization of the signal, is assessing all available signal data to determine the need for regulatory action.

“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.

“Company core data sheet (CCDS)” is a document developed by a marketing authorization holder, containing, along with safety information, material related to instructions for use, dosage, pharmacological properties, and other product-related information.

“Periodic safety update report (PSUR)” is a report for presenting an assessment of the risk-benefit ratio of a medicinal product by a marketing authorization holder in a certain period of time during the post-marketing 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 the creation of the system's structure and the planning of integrated and coordinated processes.

“Adverse event following immunization” is any adverse event that develops after immunization, regardless of the presence or absence of a relationship with the use of the vaccine. A post-vaccination complication can
be any adverse and unintended change (including abnormal laboratory findings), symptom, or disease.

“Post-authorization safety study (PASS)” is a study related to an authorized 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. The post-authorization safety study can be an interventional clinical trial or it can be conducted as an observational non-interventional study.

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

Risks identified based on the results of preclinical toxicological studies that were not observed or were rejected according to the results of clinical studies.

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 substance, or untreated group) suggests, 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.

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

“Consumer” is a person who is not an employee of the healthcare system, for example, a patient, a lawyer, a friend or relative (parent), a child of a patient.
“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 package inserts.

Examples include intentional use for another indication, in a different group of patients (e.g., a different age group), in a different route or mode of administration, or at 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.

“Compassionate use of a medicinal product” is a compassionate provision of a medicinal product to a group of patients with chronic, disabling, or life-threatening illnesses and diseases that cannot be cured using authorized medicinal products (the corresponding product must be at the stage of authorization or clinical studies).

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

“Safety concern” is a significant identifiable risk, important potential risk, or important 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, or which is being carried out at the current time, or for which the
analysis has been completed, but the final report on the clinical trial is not available.

“Direct healthcare professional communication” is a communication tool through which important information is provided directly to certain healthcare professionals designated by a marketing authorization holder or authorized 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.

“Immunization anxiety-related reaction” is an adverse event after immunization that develops due to anxiety about immunization.

“Audit findings” are results of a conformity assessment of obtained audit data with the audit criteria.

“Registry” is an organized system that uses observation methods to collect standardized data on analyzed outcomes in a population of patients with certain diseases, conditions, or exposure to certain influences.

“Audit recommendation” is a description of the course of action that management can take to correct the deficiencies and inconsistencies identified after the audit and minimize weaknesses in the management control systems.

“Risks related to 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.

“Healthcare professionals”, in the context of reporting suspected adverse reactions, are persons with medical qualifications (e.g., doctors, dentists, pharmacists, nurses, and forensic experts).
“Serious adverse reaction” is an adverse reaction that leads to death, poses a threat to the patient's life, requires hospitalization of the patient or prolonged hospitalization, leads to a persistent or severe loss of ability to work or disability, to congenital anomalies or developmental defects, requires medical intervention to prevent the development of these conditions. Any unintentional suspected transmission of an infectious agent through a medicinal product is also considered a serious adverse reaction.

“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 (e.g., by sex, age, and country), duration, severity, or outcome of the adverse reaction.

“Quality system of a pharmacovigilance system” is the organizational 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 organized by marketing authorization holders and authorized authorities of the Member States of the Eurasian Economic Union to fulfill the tasks and responsibilities for pharmacovigilance, designed to control the safety of pharmaceuticals, timely detection of all changes in the assessment of the risk-benefit ratio of
medicinal products, development, and implementation of measures to ensure the use of products when a benefit exceeds a risk.

“Spontaneous report (notification)” is a voluntary transfer by a healthcare worker or consumer to an authorized authority of a Member State of the Eurasian Economic Union, a marketing authorization holder, or another authorized organization (including the World Health Organization, 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 organized data collection.

“Reference safety information” is information on the safety of the medicinal product included in the core safety information of a marketing authorization holder (e.g., the core data sheet of the MA holder), and which the MA holder must indicate in all countries in which the medicinal product is sold, for except for cases when a Member State's authorized authority requires changes to the reference information.

“Significant change in indication” is a change in indications, which includes a change in approved indications for the use of a medicinal product, in which the new target population is significantly different from the one for which the use of the product was originally allowed, the inclusion of a new nosology, a new age group (e.g., pediatric), a change in the severity of indications from a more severe condition to a less severe one, the transition from the second line of therapy to the first line and other changes that significantly affect the risk-benefit ratio of the medicinal product.

“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 structures and processes to improve the quality system.

“Signal management” is a set of measures taken to determine the presence of new risks associated with an active substance 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, as well as to identify the 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. The objectives of pharmacovigilance are:

Prevention of unfavorable consequences of adverse reactions in humans developing after the use of authorized medicinal products following or not following the terms of the marketing authorization 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.

Therefore, pharmacovigilance is an activity directed to protecting patient and public health.

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

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

Examples of emergency safety issues include, but are not limited to, the following:

Serious safety concerns identified in ongoing or completed studies, such as unexpected increases in fatal or life-threatening adverse events.

Serious safety concerns identified based on spontaneous reports or data published in the 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, such as restricting the use of a medicinal product or temporary suspension of the marketing authorization.

The “risk-benefit ratio” concept used in these Rules is used in the meaning determined by the Rules for Approval and Examination of Medicines, approved by Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016.

2. Requirements for the quality system

2.1. Quality system

2.1.1. 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 system 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 or
objectives of the quality system. The general objectives of the
pharmacovigilance quality system are defined in paragraph 2.1.3 of these
Rules. Specific quality objectives and requirements for the
pharmacovigilance system's particular structures and processes are defined in
the relevant chapters of these Rules.

The quality system should cover the organizational structure,
responsibilities, procedures, processes and resources of the
pharmacovigilance system. The quality system should include proper
resource management, control of compliance with the requirements of the
legislation of the Member States of the Eurasian Economic Union
(hereinafter, respectively, the Member States, the Union) of international
treaties, and acts constituting the right of the Union, and document
management.

2.1.2. The quality system provides for:

Creating a system structure and planning integrated and coordinated
processes (quality planning).

Fulfilling tasks and responsibilities of the quality system following the
quality requirements (quality adherence).

Monitoring and evaluating the effectiveness of the organization and
work of the structures and processes of the quality system (quality control
and assurance).

adjusting and improving the structure and processes of the quality
system (quality improvement).
2.1.3. The general objectives of the pharmacovigilance quality system are:

Fulfillment of the requirements of the legislation of the Member State, international treaties, and acts constituting the right of the Union, and responsibilities for pharmacovigilance.

Prevention of undesirable consequences of the use of authorized medicinal products.

Ensuring the use of products when a benefit exceeds a risk.

promoting patient and public health protection.

2.2. Good Pharmacovigilance Practice Principles

2.2.1. To fulfill the general quality objectives specified in paragraph 2.1.3 of these Rules, the following principles should be adhered to when developing systems and processes, as well as in performing all tasks and responsibilities:

Ensuring that the requirements of patients, healthcare professionals, and public requirements are met concerning the safety of medicinal products.

Providing effective guidance on the implementation of the quality system and personnel motivation in relation to the objectives of the quality system.

Involvement of all employees of the organization (enterprise) in the process of supporting the pharmacovigilance system at the level of their assigned responsibilities.

Involvement of all employees of the organization (enterprise) in the continuous process of improving the quality of the pharmacovigilance system.

Organization of the resource base and 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.

Taking into account and evaluating all 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 should be considered and evaluated.

Promoting the development of effective cooperation between developers, marketing authorization holders, authorized authorities of the Member States, healthcare institutions, patients, healthcare professionals, scientific organizations, and other parties concerned in accordance with Member States' legislation.

2.3. Responsible parties for the quality system

2.3.1. All specialists involved in organizing the quality system are responsible for ensuring that the pharmacovigilance system operates in accordance with the quality system requirements. It is necessary to ensure a systematic approach to implementing and maintaining the quality system appropriately. The organization should provide a sufficient number of authorized and trained professionals with appropriate training to carry out the required amount of pharmacovigilance activities at an appropriate level.

2.3.2. A systematic approach to quality assurance should be ensured by the managers of the organization. As part of their systems approach functions, managers of organizations are responsible for ensuring:

Documenting the quality system in accordance with the requirements of these Rules.

Proper control and documentation of all changes in the pharmacovigilance system and the pharmacovigilance quality system.

Resources required for proper training.
The required resources (including the necessary premises, equipment, etc.).

Good compliance management.
Proper records management.
performing regular assessments of the pharmacovigilance system activities, including the integrated quality system and confirmation of its effectiveness. If necessary, corrective and preventive actions should be implemented.

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

Timely identification and adoption, if necessary, of corrective and preventive actions in case of non-compliance with the pharmacovigilance system quality requirements.

conducting regular audits of the system.

2.4. Personnel training

2.4.1. 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.

2.4.2. The organization shall establish and implement a training plan for pharmacovigilance specialists and 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.
Training should include introductory training and subsequent training throughout the work period in accordance with the functions performed and the tasks assigned. Training should 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 specialists should be trained to perform the procedures provided for the situations when changes in medicinal products' safety profile are detected.

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

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

2.5. Pharmacovigilance tools and equipment

2.5.1. 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.

2.5.2. Tools and equipment should 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 intended 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 organization of the functioning of information systems should provide processes for ensuring the compliance of the used terminology with the current updated versions of the corresponding used international terminology to introduce timely changes in the information systems used.

2.6. Ensuring that marketing authorization holders comply with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union.

2.6.1. To ensure compliance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union, marketing authorization holders must carry out processes to ensure the quality of the system, the objectives of which are the following:

Continuous monitoring of pharmacovigilance data, development and implementation of risk minimization 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 medical literature, identified during post-authorization studies).

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 package inserts (instructions for medical use; hereinafter, package inserts).

Fulfillment of the requirements of the legislation of a Member State, international treaties, and acts constituting the right of the Union to submit to the authorized authority of the Member State complete, accurate, and reliable information on adverse reactions and other safety information for medicinal products following the reporting time requirements established by the legislation of the Member State.

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.

Ensuring effective communication with the Member States' authorized authorities, including informing about changes in the safety profile of medicinal products and new risks, the pharmacovigilance system master file, risk management system, risk minimization measures, periodic safety update reports, corrective and preventive actions, post-authorization safety studies.

Ensuring the compliance of the information on medicinal products (summary of product characteristics, package inserts) with the state-of-the-art level.

Providing health care professionals and patients with safety information.

2.7. Ensuring by the Member States' authorized authorities of compliance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union

2.7.1. Authorized authorities of the Member States should have an appropriate process quality assurance system in place for the purposes of:

Assessing the quality of the submitted pharmacovigilance data.
Assessing and processing pharmacovigilance data in accordance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union.

Ensuring guaranteed independence in the performance of pharmacovigilance activities.

Effective information sharing with patients, health care professionals, marketing authorization holders, and the society at large.

Carrying out inspections, including a pre-authorization inspection.

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

2.8. Document Management

2.8.1. 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 safety concerns regarding the correctness of the processes, and the time of investigation and decision making.

2.8.2. The document management system should ensure the following:

- Quality management of pharmacovigilance data, including their completeness, accuracy, and integrity.
- Timely access to all records.
- Efficient internal and external data transfer.
- Storage of documents related to pharmacovigilance systems and implementing pharmacovigilance for each of medicinal products according to applicable shelf life.
2.8.3. A marketing authorization holder of a medicinal product (hereinafter, MA holder) must 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 assessment of adverse reaction reports.

Within these Rules, “reporting” means the process of transmitting, in the established form, information about adverse reactions to the authorized authorities of the Member State or expert organizations subordinated to them, whose competence includes pharmacovigilance.

2.8.4. The document management system should 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 should provide special measures at each stage of storage, processing, and transmission of pharmacovigilance data while ensuring data security and confidentiality. These measures should include a strict data access restriction, according to which access to documentation and databases should be limited by authorized persons.

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

2.8.6. The document control system should be described in the document management policy.

2.9. Quality System Documentation
2.9.1. All elements, requirements, and provisions of the quality system should be documented and arranged systematically in written guidelines and procedures such as quality plan, quality manual, and quality reports.

2.9.2. 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.

To ensure a systematic approach to planning the quality system, the organization should determine:

Quality objectives for the organization following the general objectives of the pharmacovigilance quality system in accordance with paragraph 2.1.3 of these Rules and quality objectives specific for individual structures and processes in accordance with the relevant sections of these Rules.

Methods of monitoring the effectiveness of the pharmacovigilance system.

2.9.3. The quality system should be reflected in the following documents:

Organizational structure and personnel responsibilities documentation.
Training plans and training reports.
Instructions on the conformity of management processes.
Instructions for critical pharmacovigilance processes, including ensuring process continuity; instructions on processes to be followed in an emergency, including business continuity procedures.

Process performance indicators, which are used to monitor the proper performance of pharmacovigilance functions continuously.
Reports on the audit and subsequent audit of the quality system, including the findings and results.

2.9.4. The quality system documentation should also include:
Methods for monitoring the effectiveness of the functioning of the quality system and, in particular, its ability to fulfill the quality system's objectives.
Records management policy.
Reports on the results of the performed pharmacovigilance procedures, confirming the performance of the specified stages and actions.
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.
Reports confirming the control of deficiencies and deviations from the established quality system, taking preventive and corrective measures, and evaluating the measures taken.

2.10. Additional Documentation on the MA Holder's Quality System
In addition to the required quality system documentation, a MA holder must document:
Human resource management.
Duties and functions of the pharmacovigilance system personnel.
An organizational structure that defines the hierarchical relationship of management and supervisory personnel and a resource management system.
Instructions for critical processes.
Document management system.
2.11. Additional Quality System Documentation of the Member States' authorized authorities

In addition to the required quality system documentation, the Member State's authorized authority should document the organizational structure, distribution of tasks and responsibilities of all personnel of the pharmacovigilance system, as well as identify contact persons to ensure interaction between the authorized authorities of the Member States, MA holders and persons submitting information on the risks of pharmaceuticals concerning their impact on the patient or public health.

2.12. Critical Pharmacovigilance Processes

2.12.1. Critical pharmacovigilance processes include:

Continuous monitoring of the safety profile and the risk-benefit ratio of authorized medicinal products.

Introduction, implementation, and assessment of the risk management system to assess the effectiveness of risk minimization measures.

Procedures for handling 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.

Signal management.

Development, preparation (including data evaluation and quality control), submission, and evaluation of periodic safety update reports.

Fulfillment of obligations and submission of responses to inquiries of the Member States' authorized authorities, including the submission of correct and complete information to the Member States' authorized authorities.
Ensuring interaction between pharmacovigilance and the pharmaceutical quality control system.

Information sharing with the authorized authorities of the Member States of all the safety concerns, including changes in the assessment of the risk-benefit ratio of authorized medicinal products.

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.

Ensuring the compliance of the information on the medicinal product, including the summary of product characteristics and package insert, with the current level of medical knowledge, including the conclusions made on the assessment and recommendations of the Member States' authorized authorities.

Performing all required actions in the event of a change in authorization status due to a revised safety profile.

2.12.2. The process continuity plan should include:

Determination of events that can significantly affect the personnel of the organization in general or the structures and processes of pharmacovigilance in particular.

Backup systems in case of an emergency exchange of information within the organization, with other organizations performing pharmacovigilance functions, with other developers, MA holders, and the Member States' authorized authorities.

2.13. Functioning and efficiency monitoring of the pharmacovigilance system and its quality system

2.13.1. Methods for monitoring the activity and efficiency of the pharmacovigilance system should include:
Review and analysis of the system by responsible managers.
Audits.
Control of compliance with requirements.
Inspections.

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

2.13.2. To carry out monitoring in the organization, 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.

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

2.13.3. 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 should include an audit of a pharmacovigilance system that has an integrated quality system. Recommendations on audit methods and processes are included in paragraph 5 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 organizations or persons to whom the MA holder has delegated pharmacovigilance functions since they are part of the MA holder's pharmacovigilance system.
Based on the pharmacovigilance system and the pharmacovigilance quality system monitoring results, including the audit results, corrective and preventive actions are developed and implemented if necessary.

2.13.4. Authorized authorities of the Member States should ensure monitoring the fulfillment of the pharmacovigilance functions and duties by the MA holders established by the legislation of the Member States. Monitoring measures include inspections of MA holders by the Member States' authorized authorities.

2.14. Pharmacovigilance Obligations of MA Holders

MA holders are responsible for fulfilling the tasks and responsibilities for pharmacovigilance determined by these Rules and the legislation of the Member States requirements to guarantee the fulfillment of obligations and, if necessary, take the required pharmacovigilance activities concerning authorized medicinal products. To this end, MA holders should ensure the functioning of the pharmacovigilance system in the Member States territory, including the implementation of an appropriate and effective pharmacovigilance quality system.

Under certain circumstances, MA holders may organize more than one pharmacovigilance system, such as a separate pharmacovigilance system for certain groups of medicinal products (e.g., vaccines, over-the-counter medications).

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 authorizations for all authorized medicinal products. A MA holder is also responsible for developing, implementing, and maintaining risk management systems adapted for each of the authorized medicinal products.
Requirements for the structures and processes of the MA holder's pharmacovigilance system are determined in the relevant sections of these Rules.

2.15. Pharmacovigilance Officer

2.15.1. In the Member States, a MA holder must appoint and maintain at all times a pharmacovigilance officer having the required qualifications. The MA holder provides the pharmacovigilance officer's name and contact information to the Member States' authorized authorities. When this information is changed, the MA holder must immediately inform the Member States' authorized authorities within a period of not more than 30 calendar days.

2.15.2. The job description should determine the pharmacovigilance officer's responsibilities. The pharmacovigilance officer's hierarchical position and interaction should be determined in the MA holder's organizational structure at the management personnel level.

2.15.3. Information about the pharmacovigilance officer must be included in the MA holder's pharmacovigilance system master file.

2.15.4. Each pharmacovigilance system can only have one pharmacovigilance officer. A 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 pharmacovigilance officer can perform all own responsibilities. In addition to the appointment of a pharmacovigilance officer, the Member States' authorized authorities may require the assignment of a contact person for pharmacovigilance subordinate to the pharmacovigilance officer. The contact person can act as a pharmacovigilance officer. The MA holder's
pharmacovigilance system organization in the Member State territory must ensure that the requirements are met the legislation of the Member States concerning pharmacovigilance, and international treaties and acts constituting the right of the Union, effective interaction with the Member State's authorized authority, and the absence of obstacles in the collection and submission of information about the identified adverse reactions in the Member State territory.

2.15.5. A MA holder grants a pharmacovigilance officer sufficient authority to manage the pharmacovigilance activity and the quality system. The MA holder provides the 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 should allow the pharmacovigilance officer to make changes to the system, risk management plans, and prepare regulatory actions in response to emergencies to change the safety profile.

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

- On emergencies 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.

- About ongoing and completed clinical studies and other studies that the MA holder knows about and that may be relevant to the safety of medicinal products.
From sources other than those of the MA holder, for example, sources with which the MA holder has contractual agreements.

The pharmacovigilance procedures that the MA holder develops at each level to ensure consistency and compliance within the organization.

2.15.7. A 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 pharmacovigilance officer has the authority to initiate an audit if necessary. The management personnel will provide the pharmacovigilance officer with a copy of the corrective and preventive action plan after each audit so that the pharmacovigilance officer can be sure that the appropriate corrective action is being taken.

2.15.8. A MA holder provides an opportunity for a 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 authorized authority. The MA holder must take appropriate organizational measures that allow the pharmacovigilance officer to access the adverse reactions database, including outside working hours.

2.15.9. A MA holder ensures that a 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 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 pharmacovigilance officer is informed about the parties' contractual obligations in terms of
pharmacovigilance activities and the safety data exchange and gives him the right to amend this part of the contractual obligations. The 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 should be taken into account when making a decision and determining the contractual obligations of the parties.

2.15.10. A MA holder ensures that a pharmacovigilance officer is informed about the intention to establish cooperation with another MA holder, an organization, or an individual who may directly or indirectly influence the pharmacovigilance system, before the conclusion of contractual agreements in a time sufficient for the pharmacovigilance officer to perform the assessment the possible impact of this collaboration on the pharmacovigilance system. The MA holder empowers the pharmacovigilance officer to make proposals and changes in contractual obligations related to the pharmacovigilance system.

2.16. Qualification of a Pharmacovigilance Officer

2.16.1. A pharmacovigilance officer must have the appropriate theoretical and practical knowledge to carry out pharmacovigilance activities. The pharmacovigilance officer must have the skills to manage pharmacovigilance systems and conduct expertise or have access to expertise in medicine, pharmaceutical sciences, epidemiology, and biostatistics.

2.16.2. A MA holder conducts training for a pharmacovigilance officer in the area of their pharmacovigilance system before the pharmacovigilance officer's appointment. The training and its results must be properly documented.
2.17. Functions of a Pharmacovigilance Officer in the Union

2.17.1. A pharmacovigilance officer is a natural person.

2.17.2. A pharmacovigilance officer, appointed by a MA holder, must be qualified in accordance with paragraph 2.16 of these Rules and be at the permanent disposal of the MA holder. The pharmacovigilance officer must reside and work in one of the Member States. The MA holder must ensure that there is a backup agreement in case of the temporary absence of the pharmacovigilance officer, with the definition of the person performing the pharmacovigilance officer's duties in his absence. The MA holder must ensure that the person substituting the pharmacovigilance officer can fulfill the pharmacovigilance duties and the availability of this person when using the contact details of the pharmacovigilance officer.

The 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 quality system of the pharmacovigilance 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 pharmacovigilance officer should have the authority and responsibility concerning the pharmacovigilance system master file to ensure and improve compliance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union.

2.17.3. For medicinal products covered by the MA holder's pharmacovigilance system, a pharmacovigilance officer has the following responsibilities:

Review of drug safety profiles and identified safety concerns.
Being fully informed about the conditions and obligations established when getting marketing authorization and other obligations related to the safety or safe use of medicinal products.

Having complete information on risk minimization measures.

Taking part in the assessment and approval of the protocols of post-authorization safety studies.

Having complete information on post-authorization safety studies, the conduct of which is appointed by the Member States' authorized authority, including the results of such studies.

Complementing risk management plans.

Ensuring the performance of pharmacovigilance functions and submitting all documents related to pharmacovigilance according to the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union.

Ensuring the required quality, including accuracy and completeness of pharmacovigilance data submitted to the Member States' authorized authorities.

Providing complete and timely responses to requests from the Member States' authorized authorities for the provision of additional information necessary to assess risks and benefits of medicinal products.

Submitting any information related to the assessment of the risk-benefit ratio to the authorized authorities of the Member States.

Assistance in the preparation of regulatory actions when safety concerns are identified (e.g., changes in recommendations for medical use, urgent restrictions, and notification of patients and health care professionals).

Functioning as a single contact person for pharmacovigilance for the Member States' authorized authorities and a contact person for pharmacovigilance inspections available 24 hours a day.
2.17.4. A 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 pharmacovigilance officer should have information on the validation status of the adverse drug reactions database, including any deficiencies identified during validation and corrective actions taken. The pharmacovigilance officer should also be aware of any significant changes made to the database (e.g., changes that may impact the pharmacovigilance activity).

The pharmacovigilance officer may delegate the implementation of specific tasks under his supervision to persons with appropriate qualifications and training, for example, acting as experts on the safety of certain medicinal products, provided that the 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 should be properly documented.

2.18. Specific quality system processes from MA holders

2.18.1. A MA holder develops additional specific quality system processes for:

Submitting data on adverse reactions to the databases of the Member States and the Union within the time limits established by the legislation of the Member States, international treaties, and acts constituting the right of the Union.

Systematically or regularly monitoring the terminology used.
Saving the pharmacovigilance system master file documents as long as the system described in the pharmacovigilance system master file exists and for at least 5 years after its termination.

Saving pharmacovigilance data and documents related to authorized medicinal products for at least 10 years after the termination of approval.

Updating information on medicinal products following the latest scientific knowledge, including an assessment of the safety profile and the risk-benefit ratio, as well as recommendations posted on the websites of the authorized authorities of the Member States in the information and telecommunications network “Internet.” To this end, the MA holder constantly checks the websites of the Member States' authorized 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.

2.18.2. During the storage period of the documents, MA holders ensure the recoverability of documents.

2.18.3. 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.

2.18.4. In the event of a takeover by another organization of the MA holder's business, all documents must be transferred and retained in full.

2.19. Quality system requirements for delegation by a MA holder of pharmacovigilance functions performed
2.19.1. A MA holder may delegate all or part of his/her pharmacovigilance tasks, including the pharmacovigilance officer's functions, to another organization or person (if the exact requirements can be applied to such a person as to the organization). 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.

2.19.2. If a MA holder delegates certain pharmacovigilance tasks to another organization, the MA 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 another organization to which tasks are delegated.

2.19.3. When delegating tasks to another organization, a MA holder provides detailed, precise, and constantly updated documentation of the contractual agreements between the MA holder and the other organization, describing the arrangements for delegated tasks and each other's responsibilities. The description of the delegated activities and (or) services should be included in the pharmacovigilance system master file, including a list of contract organizations in the annex to the master file. Another organization may be subject to inspection for compliance with the performed pharmacovigilance activities in accordance with the requirements of these Rules at the discretion of the authorized authority of the Member State.

2.19.4. Contractual agreements for the delegation of pharmacovigilance tasks should ensure that the parties comply with the pharmacovigilance legislation's requirements. A MA 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 functions. To
control the implementation of contractual agreements on pharmacovigilance, it is recommended that the MA holder performs regular audits of organizations to which the pharmacovigilance functions have been delegated.

2.20. General responsibilities for pharmacovigilance within international treaties and acts constituting the right of the Union.

2.20.1. Authorized authorities of the Member States are responsible for implementing pharmacovigilance tasks assigned to them by the legislation of a Member State, international treaties, and acts constituting the right of the Union. To this end, each Member State's authorized authority ensures the pharmacovigilance system's functioning, creates and applies an appropriate, effective quality system for the pharmacovigilance activities performed.

2.20.2. Member States cooperate to continuously improve pharmacovigilance systems to achieve high standards of public health protection, including pooled resources to optimize the use of the existing resource base within the Union.

2.20.3. Member States define contacts to simplify the interaction of the Member States' authorized authorities, MA holders, and persons submitting pharmacovigilance information.

2.21. Functions of the authorized authorities of the Member States

2.21.1. Each Member State should designate an authorized authority responsible for the implementation of pharmacovigilance activities.

2.21.2. Each Member State's authorized authority must 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 Member State's authorized authority is
responsible for monitoring each authorized medicinal product's safety, regardless of the registration procedure applied.

2.21.3. The tasks and responsibilities of the Member States' authorized authorities for pharmacovigilance include cooperation in the detection of signals and the application of risk minimization measures when making appropriate decisions. If it is necessary to take urgent measures to ensure the protection of public health concerning a medicinal product authorized using the mutual recognition procedure, the authorized authority of the Member State concerned takes the necessary steps, including withdrawal from the market or stopping use in its territory.

2.21.4. Authorized authorities of the Member States are responsible for monitoring the fulfillment by MA holders of their pharmacovigilance obligations for medicinal products on their territory, including inspections of the MA holders' pharmacovigilance systems, regardless of the authorization procedure for medicinal products in the Member States territory. An authorized authority of each Member State ensures the submission of pharmacovigilance data to authorized authorities of other Member States in accordance with the legislation of the Member State, international treaties, and acts constituting the right of the Union.

2.22. Pharmacovigilance preparedness planning in case of public health emergencies

2.22.1. Pharmacovigilance systems of MA holders and the Member States' authorized authorities should be adapted to public health emergencies, including the development of an emergency preparedness plan.
A public health emergency is a public health threat recognized by the World Health Organization (WHO) or the Member States' authorized authorities.

The requirements for the pharmacovigilance system in case of public health emergencies in each of the cases are determined by the Member States' authorized authorities and are communicated to the MA holders and the public. Authorized authorities of the Member States publish notices of emergencies on their official websites.

3. Pharmacovigilance System Master File

3.1. Structures and Processes of the Pharmacovigilance System Master File

3.1.1. The pharmacovigilance system master file is intended to describe the pharmacovigilance system and documentary confirmation of its compliance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union. The pharmacovigilance system master file allows properly planning and conducting the pharmacovigilance system audits by a MA holder and inspections by the Member States' authorized authorities. The pharmacovigilance system master file includes an overview of the MA holder's pharmacovigilance system, making it possible to make its general assessment by the Member States' authorized authorities while getting the marketing authorization and at the post-marketing period.

3.1.2. Drawing up a pharmacovigilance system master file and updating the information contained in it allow a MA holder and the pharmacovigilance officer for the following:
Making sure that the pharmacovigilance system is implemented in accordance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union.

Confirming the compliance of the system with the current requirements.

Obtaining information about system deficiencies or identify non-compliance with requirements.

Obtaining information about the risks or inefficiency of the implementation of certain pharmacovigilance activity areas.

3.1.3. 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 MA holder's pharmacovigilance system, the submission of the pharmacovigilance system master file, and the chronology of changes facilitate the planning and effective conduct of inspections by the authorized authorities of the Member States based on the risk assessment method.

3.2. Approval and Maintenance of a Pharmacovigilance System Master File

3.2.1. Summary of a MA Holder's Pharmacovigilance System.

In accordance with the requirements of the Rules for Approval and Examination of Medicinal Products, approved by Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016, a summary of a MA holder's pharmacovigilance system is presented in Section 1.10 of Module 1 of the Drug Master File if, upon the previous submission by the MA holder, the MA holder's pharmacovigilance system master file was submitted to the Member State's authorized authority. The
summary of a pharmacovigilance system should include the following elements:

Written confirmation by a MA holder of the fact that he has a pharmacovigilance officer at his disposal. Where the MA holder is established outside the Member States, written confirmation shall be included that there is a contact person for pharmacovigilance within the Member State.

Information on a Member State where the pharmacovigilance officer lives and performs his (her) functions.

Contact details of the pharmacovigilance officer and the contact person for pharmacovigilance (if applicable).

Declaration signed by the MA holder committed to performing activities and obligations listed in the Rules of the Good Pharmacovigilance Practice of the Union.

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

3.2.2. Location of a Pharmacovigilance System Master File.

The pharmacovigilance system master file must be located in the Member States territory, either at the place where the main pharmacovigilance activity is performed or where the pharmacovigilance officer works, regardless of the format (electronic or hard copy). The Member State's authorized authority must be informed about the location of the pharmacovigilance system master file and must immediately, within not more than 30 days, be notified of any changes in its location. The required information on the location of the master file includes an indication of the location (address) of the MA holder or a third party by agreement. This address may differ from the applicant's or the MA holder's address, for example, if the address of another MA holder's office is indicated or a third party performs the main activity following the agreement. When determining
the main location for the pharmacovigilance activity, the MA holder should consider the best location for the pharmacovigilance system as a whole. The MA holder must have appropriate justification for deciding on the location of the master file. In a situation where the main activity is carried out outside the Union, or it is impossible to determine the main location, by default, the location of the master file is the place of business of the pharmacovigilance officer.

3.2.3. Transfer of responsibilities for the pharmacovigilance system master file.

3.2.3.1. The transfer or delegation of responsibilities and activities for the pharmacovigilance system master file should be documented and monitored to confirm that a MA holder fulfills his duties. The pharmacovigilance officer should be notified about the pharmacovigilance system master file changes to ensure that changes improve the system. The types of changes that should be immediately reported to the pharmacovigilance officer are:

Changes made to a pharmacovigilance system master file, or a change in its location, information about which must be reported to the authorized authorities of the Member States.

Adding corrective and (or) preventive actions to the pharmacovigilance system master file (e.g., based on the results of audits and inspections) and managing deviations from the processes identified in the pharmacovigilance quality management system.

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).
Changes in the established agreement on the submission of the pharmacovigilance system master file to authorized authorities of the Member States.

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

Inclusion of medicinal products in the pharmacovigilance system, for which the pharmacovigilance officer is responsible.

Changes concerning medicinal products included in the pharmacovigilance system, which may require an increase in the number of pharmacovigilance activities performed, for example, addition of indications, implementation of studies, inclusion of additional countries.

3.2.3.2. The pharmacovigilance officer must confirm in writing his notification regarding changes in the transfer of responsibilities for the pharmacovigilance system to the pharmacovigilance officer.

3.3. Description of Pharmacovigilance Systems

The pharmacovigilance system master file shall describe the MA holder's pharmacovigilance system for one or more medicinal products. The MA holder can apply different pharmacovigilance systems to different categories of medicinal products. Each such system should be described in a separate pharmacovigilance system master file. The pharmacovigilance system master file should generally cover all medicinal products of the MA holder for which the marketing authorization has been applied.

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, one pharmacovigilance system master file describing each system is submitted.

The MA holder must be appointed a pharmacovigilance officer responsible for creating and maintaining the pharmacovigilance system described in the pharmacovigilance system master file.

If several MA holders use one pharmacovigilance system, each MA holder 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 (for example, to a license partner or subcontractor), part or all of the pharmacovigilance activities 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 activity was delegated following an agreement on access to this information by the MA holder and authorized authorities of the Member States. The MA holder must ensure that the reference files' content complies with the pharmacovigilance system applicable to the medicinal product.

Where appropriate, the annex contains 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 pharmacovigilance officer and related medicinal products.

In the summary information submitted to the Member States' authorized authorities, several locations of one pharmacovigilance system master file cannot be indicated.

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

When delegating activities on the pharmacovigilance system and its master file, 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 authorized authorities of the Member States upon request. There should be written agreements describing the roles and responsibilities for the pharmacovigilance system master file, its submission and maintenance, and the implementation of pharmacovigilance in accordance with the requirements of the legislation of a Member State.

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' authorized authorities should be specified in written agreements. It is important for the MA holder to be satisfied that the pharmacovigilance system for the products meets the necessary requirements.

3.4. Mandatory Information in a Pharmacovigilance System Master File

A pharmacovigilance system master file should include documents describing the pharmacovigilance system. The pharmacovigilance system master file's content should reflect the availability of safety information of medicinal products authorized in the Member States. The master file must have a table of contents for navigation in the document. The main principle of the formation of 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. The 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.

3.4.1. Section of the Master File about a Pharmacovigilance Officer.

Information about a pharmacovigilance officer in a pharmacovigilance system master file should include:

Description of the responsibilities to ensure that the pharmacovigilance officer has appropriate authority over the pharmacovigilance system to ensure, assist and improve compliance.

Summary with core information on the role of the pharmacovigilance officer, a description of his qualifications, and experience related to pharmacovigilance activities.

The pharmacovigilance officer's contact information, which should include the last name, first name, patronymic (if any), postal address of stay, telephone, fax numbers, e-mail address, and postal business address.

Information on the use of standby agreements in the absence of the pharmacovigilance officer. If specific tasks of the pharmacovigilance officer are delegated to another performer, the list of delegated tasks should be included in the annexes with an indication of the description of the delegated activity and the persons to whom it was delegated.

Description of the area of responsibility of the contact person for pharmacovigilance, if that person is present at the Member State level.

3.4.2. Section of the Pharmacovigilance System Master File on the Organizational Structure of a MA Holder.

3.4.2.1. It is necessary to describe the organizational structure of the relevant pharmacovigilance system of a MA holder. The description should give a clear idea of the organizations involved, the main structural units
involved in pharmacovigilance, and the relationship between organizations and structural units related to the performance of pharmacovigilance activities. The following information should be provided in the pharmacovigilance system master file:

- the organizational structure of a MA holder, including an indication of the position of the pharmacovigilance officer in the organization;

- Address of the location 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-marketing and post-authorization studies, and management of changes made to the safety information of a medicinal product.

3.4.2.2. Section of a pharmacovigilance system master file on delegated pharmacovigilance activities.

3.4.2.2.1. A pharmacovigilance system master file must contain a description of the activities and (or) services for the fulfillment of pharmacovigilance obligations delegated by a MA holder.

3.4.2.2.2. The information in the section should contain confirmation of the relationship with other organizational structures (e.g., an agreement on joint marketing of a medicinal product, an agreement on the implementation of pharmacovigilance activities by contractors, as well as other commercial agreements). It is necessary to locate and describe the system of existing agreements for delegated pharmacovigilance activities. The description of the agreements system can be drawn up in the form of a list or table. When describing the agreements system in the form of a table, information is provided on the parties concerned, the obligations undertook, medicinal products for which pharmacovigilance is performed, and the Member States
territory where pharmacovigilance is conducted. When describing the agreements system in the form of a list, it is structured by the types of services used (e.g., the provision of medical information, audit services, provision of patient support programs, processing of study data), types of commercial agreements (drug distribution agreement, joint marketing agreement, agreement on the right of common to the Drug Master File, etc.) and types of technical support for pharmacovigilance activities (placement of computerized systems on the provider's servers, archiving and storing pharmacovigilance data, etc.). Copies of individual agreements are submitted at the request of the Member States' authorized authorities or during the inspection and audit; a list of them is given in the annexes.

3.4.3. Section of the Master File on the Safety Data Sources.

3.4.3.1. The description of the main departments dealing with the collection of adverse reaction reports should include all parties responsible for collecting reports received on request and spontaneous reports of adverse drug reactions authorized in the territories of the Member States. The description should include the location of the health information and the affiliated offices of the organization. This information can 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, 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 authorized authority should indicate the units and (or) third parties involved in the procedure.
3.4.3.2. Sources of safety information should 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 should be able to provide these lists upon request when conducting pharmacovigilance system inspections, audits, or system evaluations performed by a pharmacovigilance officer. The list should describe (globally) the status of each study or program, the respective state, medicinal products, and main objectives. Interventional and non-interventional studies should be indicated separately according to the active substance of the medicinal products. The list should 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.

3.4.4. Section of the master file on computerized systems and databases.

3.4.4.1. The pharmacovigilance system master file should describe the location, functionality, and operational responsibility for the computerized systems and databases used to obtain, verify, report safety information and assess its compliance with the assigned tasks.

3.4.4.2. If several computerized systems or databases are used, their applicability to pharmacovigilance activities should be described in such a way that the scope of computerization within the pharmacovigilance system is understood. Besides, the validation status of the main aspects of the functionality of the computerized 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 should 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.

3.4.5 Section of the Master File about Processes.

3.4.5.1. An important component of a pharmacovigilance system is the availability of written standard procedures at the place of business. The subparagraphs of Section 2 of these Rules describe the required minimum set of written pharmacovigilance procedures. The pharmacovigilance system master file should describe the available procedure documentation (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, paper files at the place of receipt).

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

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 clinical departments, etc.

Risk management system and monitoring of the results of the implementation of risk minimization measures. If several departments are involved in this process, the order of their interaction is determined by written procedures or agreements.
Collection, verification, obtaining follow-up information, assessment, and presentation of information on individual cases of adverse reactions. The procedures under this section should clearly distinguish between local and international activities.

Planning, drawing up and submitting periodic safety update reports.

Providing consumers, healthcare professionals, and authorized authorities of the Member States with safety information.

Making safety-related changes in the summary of product characteristics and package insert. The procedures should cover internal and external communication.

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

3.4.5.4. Data on other activities should 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 a pharmacovigilance officer, response to requests from authorized authorities of the Member States for the provision of information, literary searches, 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 should include the procedure document number, title, effective date, and type of document (for all standard operating procedures, work instructions, manuals, etc.). Procedures that have been delegated to third parties must be properly identified. Documents related to specific local procedures may not be included in the general list of procedural documents but must be provided at the request of a relevant authorized authority at the state level, indicating the countries in which these procedures are used.
3.4.6. Section of the master file on the functioning of the pharmacovigilance system.

The pharmacovigilance system master file should 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:

A description of the procedure for assessing the correctness of individual case safety reports submitted. Figures (graphs) must be presented, confirming the timeliness of the submission of information in accordance with the requirements of the legislation of the Member States.

Description of the performance indicators used to control the quality of the information provided and pharmacovigilance activities. Such indicators include information received from authorized authorities of the Member States regarding the quality of reporting adverse reactions, PSURs, or other reported data;

Analysis of the timeliness of submission of PSURs to authorized authorities of the Member States (the annex should reflect the latest data used by a MA holder to assess compliance with the requirements).

Analysis of the methods used to assess the timeliness of safety changes compared to the deadlines set by authorized authorities, including a description of the necessary safety changes that have been identified but have not yet been submitted to the authorized authority.

If appropriate, an analysis of the fulfillment of obligations following the risk management plan or other obligations or requirements established during approval 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.

3.4.7. Section of the Pharmacovigilance Master File on the Quality System.

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

3.4.7.1. Control of Documents and Records.

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 should be provided, and an overview of the procedures applied to other records documents of the pharmacovigilance quality system.

3.4.7.2. Procedural Documents.

The description of the procedural documentation should include:

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 levels of the functioning of the pharmacovigilance system in the organization, as well as the elements of document control that are applied in regarding access to procedural documentation, implementation, and maintenance.

Information on the documentation systems applicable to relevant procedural documents under the control of third parties.

3.4.7.2. Training.

A description of resource management during pharmacovigilance activities is provided:
Organizational structure with the number of people involved in implementing pharmacovigilance activities (in the equivalent of full personnel units), which can be presented in the section describing the organizational structure.

Information on the location of personnel carrying out the organization and implementing certain types of pharmacovigilance activities is provided in the pharmacovigilance system master file and its annexes, a list of contact persons submitting safety data. Information on the location of personnel should be accompanied by a description of the personnel and the respective locations of the activity to justify the training organization system.

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

Personnel should 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.

3.4.7.3. Audit.

Information about the audit of the quality assurance system in the pharmacovigilance system should be included in the pharmacovigilance system master file. The annex should include a description of the pharmacovigilance system audit scheduling method reporting mechanisms and a current list of planned and completed pharmacovigilance system audits, included in an annex to the master file. This list should include the dates of audits and submission of reports on the results of audits, the scope and status of audits by service providers, specific pharmacovigilance activities or locations of pharmacovigilance functions, and operational areas of engagement relevant to meeting obligations. The list should include data for a period of 5 years.
The pharmacovigilance system master file should also contain comments on audits, during which significant results were obtained. This means that the list of audits performed should indicate the assessed results as significant or critical inconsistencies and a summary of the corrective or preventive action plan for these inconsistencies with deadlines. Reference should be made to the full audit report, documents with the corrective and preventive action plan. If 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 should be included that “the corrective and preventive action plan(s) should be agreed.” In the annex, in the list of audits performed, audits with pending approval work should be indicated. Comments and related corrective and preventive actions should 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 should be recorded in the appropriate logbook.

As a means of managing the pharmacovigilance system and providing the basis for an audit or inspection, the pharmacovigilance system master file should 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 can be included in the form of a checklist with deviation report numbers, dates, and a description of the corresponding procedures performed.
3.4.8. Annex to the pharmacovigilance system master file.

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

- a list of medicinal products authorized by a MA holder in the Member States and in third countries to which the pharmacovigilance system master file applies, including the names of medicinal products, international non-proprietary names of active substances, and the name of the state in which the marketing authorization is valid.

The list of medicinal products approved in the Member States must include the marketing authorization number, as well as for each approval the following information:

- Type of approval procedure (e.g., approval of medicinal products at the national level, through a mutual recognition procedure or a decentralized procedure).

- Reference Member State.

- The presence on the market of the Member States.

- Third countries in which the product is authorized or on the market.

The list should be structured according to the active substances and, if appropriate, should contain an indication of the existence of specific requirements for the safety control of the medicinal product (e.g., the introduction of risk minimization measures described in the risk management plan or established as a condition for approval of the medicinal product; changing the frequency of submission of periodic safety update report; inclusion in the list of drugs subject to additional monitoring).

For marketing authorizations 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 obligations for this marketing authorization, the
pharmacovigilance system master file should 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.

In the case of joint pharmacovigilance systems, 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 provide this information, one list can be used, indicating the name of the MA holder(s) for each medicinal product, or, alternatively, separate lists describing the products of each of the MA holders.

List of written standards and quality system procedures for the pharmacovigilance system.

List of contractual arrangements related to delegated pharmacovigilance activities, including relevant medicinal products and territories.

List of tasks delegated by a pharmacovigilance officer.

List of all completed audits over a 5-year period and a list of planned audits.

List of indicators for assessing pharmacovigilance activities (when applicable).

List of other master files of the pharmacovigilance system maintained by the MA holder (when applicable).

List of other master files of the MA holder (if applicable). The list should include the number of the pharmacovigilance system master file and information about the pharmacovigilance officer responsible for this pharmacovigilance system. If this pharmacovigilance system is operated by another party that is not the MA holder, information on this pharmacovigilance service provider is indicated;
Log of all changes made to the pharmacovigilance system master file content for the last 5 years, except for information regarding the requirements of indents 3 to 6 of paragraph 3.4.1. of these Rules and information included in the annexes to the pharmacovigilance system master file. The information on the change should include an indication of the date of the change, the person responsible for the change, and a description of the change made to the pharmacovigilance system master file.

3.5. Change Control, Versioning, and Archiving

3.5.1. MA holders should ensure that the change management system is applied in the pharmacovigilance system master file and have reliable processes for obtaining information on relevant changes on time and then properly updating the master file. Authorized authorities of the Member States may request information on important changes in the pharmacovigilance system, which particularly may include the following:

a. Changes in the safety database(s) of the pharmacovigilance system, 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.

b. Changes in the provision of significant pharmacovigilance services, especially regarding important contractual agreements for the safety data submission.

c. Such organizational 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 must ensure that the pharmacovigilance officer is informed about these changes.

3.5.2. Changes in the pharmacovigilance system master file should 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 regarding the requirements of indents 3 to 6 of paragraph 3.4.1. of these Rules and information included in the annexes of the pharmacovigilance system master file.

The history of changes in the information 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 contents of annexes. Information in annexes that is regularly updated, such as lists of medicinal products, standard operating procedures, or compliance indicators, may include results from controlled systems (such as electronic document management systems or authorized authorities' databases). Previous versions of this information on annexes may be managed outside of the master file, provided that the history of changes is maintained and available to the authorized authorities of the Member States upon request. If the master file has not been requested by an authorized authority or has not been modified for a specified period of time (e.g., if changes to contents of annexes managed outside the scope of the master file), it is recommended that periodic compliance review 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 pharmacovigilance officer must have access to updated and reliable information about the pharmacovigilance
system; therefore, the MA holder must have constant access to the pharmacovigilance system master file, including the information contained in annexes (or using the pharmacovigilance system master file itself, or through access to the systems used to create contents of annexes).

3.5.3. MA holders should 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, for a correct understanding, additional assessment of the functioning and focus of the pharmacovigilance system in the previous stages may be required.

3.5.5. When making changes to the pharmacovigilance system master file, it is also necessary to take into account joint pharmacovigilance systems and delegated pharmacovigilance activities. Adequate change control involves recording the date and context of notifications of changes made for authorized authorities of the Member States, pharmacovigilance officers, and third parties.

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

3.6. Presentation of the pharmacovigilance system master file

The pharmacovigilance officer should have permanent access to the pharmacovigilance system master file. Authorized authorities of the Member States should be provided with permanent 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, revised
taking into account the experience gained, technical and scientific progress,
changes in regulatory standards. A MA holder must provide authorized
authorities of the Member States with access to the pharmacovigilance
system master file within 7 working days after receiving the relevant request.
The MA holders must provide direct access to the authorized authorities of
the Member States to the pharmacovigilance system master file at the
indicated location of the pharmacovigilance system master file or the place of
activity of the pharmacovigilance officer.

3.6.1. Format and structure of the pharmacovigilance system master file

The pharmacovigilance system master file can be in electronic form,
provided that it is possible to submit a clearly structured hard copy at the
request of authorized authorities of the Member States. In any format, the
pharmacovigilance system master file should be in a readable, complete, and
accessible form, allowing for the assessment of all documents and
traceability of changes. It may be necessary to restrict access to the
pharmacovigilance system master file to properly control its content and
assign responsibilities for managing the pharmacovigilance system master
file (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 should be included in the annexes and
described in the index. The documents and data of the master file must be
presented in the following headings and, if they are in a hard copy, must be
presented in the indicated order:

Title page must contain the numbers of the pharmacovigilance system
master file, the name of the MA holder, the authorized person responsible for
the described pharmacovigilance system, the names of other MA holders
(using this pharmacovigilance system), a list of master files for the MA holders (for medicinal products with a different pharmacovigilance system), the date of preparation or the last update of the pharmacovigilance system master file.

The headings used in section 3.4 of these Rules should be used to indicate the main sections of the content of the master file. Minimum required contents of annexes to the master file is set out in paragraph 3.4.8 of these Rules, additional information may be included in the annexes to the master file, provided that the requirements for the contents of the main sections are met. Annexes include the following information:

Information about the pharmacovigilance officer (Annex A).

List of tasks delegated to the pharmacovigilance officer or the corresponding procedural document.

Biographical data of the pharmacovigilance officer and related documents; additional contact details, if necessary.

Organizational structure of the MA holder (Annex B).

Lists of contracts and agreements.

Safety data sources (Annex C).

Lists describing the sources of safety data, such as affiliates and third-party contacts.

Computerized 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 (Anne G).

Audit plan.
List of conducted and completed audits.
Medicinal products (Annex H).
List of medicinal products covered by the pharmacovigilance system.
Comments in regard to MA holders.
Control of records and documentation (Annex I).
Changelog.

Documentation of the history of changes in the contents of annexes indexed according to annexes A to I and their contents if this 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 contents of an annex, there is no need to provide pages with empty content, however, annexes that are provided must still be named following the above format. For example, Annex E should not be renamed Annex D when an annex not related to the computerized systems and databases is used; Annex E should simply be called “unused” in contents to indicate the lack of content.

3.7. Responsibilities of the Participants in the Pharmacovigilance System


3.7.1.1. MA holders must 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 records pharmacovigilance activities for one or more authorized medicinal products. A MA holder must appoint one pharmacovigilance officer responsible for creating and operating the pharmacovigilance system described in the pharmacovigilance system master file.
3.7.1.2. When applying for marketing authorization of a medicinal product, the applicant must have at his disposal a description of the pharmacovigilance system that will operate on the territory of the Union or the territory of an individual Member State. During the evaluation of the marketing authorization application, the applicant may be required to submit a copy of the pharmacovigilance system master file for review.

3.7.1.3. A MA holder is responsible for creating a pharmacovigilance system master file, which includes the Member States territory and registering the location of the master file with authorized authorities of the Member States when applying for marketing authorization 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.

3.7.1.4. The work on creating, maintaining, and submitting the pharmacovigilance system master file to the Member States' authorized authorities can be transferred to a third party; still, a MA holder retains full responsibility for compliance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union. Maintaining the pharmacovigilance system master file in operable working condition and access (constant access for audit and inspection) can be delegated; still, the MA holder is on an ongoing basis responsible for ensuring that this function is performed at a level that meets the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union.

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

3.7.2. Authorized authorities of the Member States.

3.7.2.1. Authorized authorities of the Member States are responsible for overseeing the pharmacovigilance systems of MA holders. As part of this obligation, the authorized authorities assess the summary information about the pharmacovigilance system included in the Drug Master File when applying for marketing authorization. A complete pharmacovigilance system master file can be requested at any time (e.g., if there are questions about the pharmacovigilance system, the safety profile of a medicinal product, or 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.

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

3.8. Availability of the Pharmacovigilance System Master File

3.8.1. Pharmacovigilance system master file is maintained in operable condition, available for a pharmacovigilance officer. It must also be available for inspection at all times, regardless of whether a prior notification has been made or not.
3.8.2. A MA holder maintains and submits, at the request of the Member State's authorized 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 presented in a readable form in electronic format or hard copy.

3.8.3. 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 must 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 authorized authority within 7 working days after receiving the relevant request.

3.8.4. Pharmacovigilance system master file is usually not requested during the assessment of new marketing authorization applications of a medicinal product (that is, before approval); still, it can be requested in special cases, particularly in the case of a new pharmacovigilance system, or when safety concerns of a medicinal product, or questions on compliance with the requirements of the legislation of a Member State, international treaties, and acts constituting the right of the Union concerning pharmacovigilance.

4. Inspection of the Pharmacovigilance System

4.1. Introduction

4.1.1. To confirm the fulfillment of the MA holders' pharmacovigilance obligations, the authorized authorities of the Member States are obliged to conduct pharmacovigilance inspections of the MA holders or other organizations involved by the MA holders to fulfill the pharmacovigilance
obligations. Pharmacovigilance inspections should be carried out by inspectors appointed by the Member States' authorized authorities, empowered to inspect the premises, get acquainted with materials, documents, and the pharmacovigilance system master file from the MA holder or other organizations involved by the MA holder to fulfill the pharmacovigilance obligations. At the request of the Member State's authorized authority, the MA holder is obliged to submit a pharmacovigilance system master file, which will be used to inform about the conduct of inspections.

4.1.2. The objectives of pharmacovigilance inspections are:

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).

4.1.3. An authorized authority of a Member State has the right to conduct pharmacovigilance inspections before approval 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 Member States' authorized authorities interact to exchange information regarding the planned inspections and the results of inspections that have already been carried out. Concerning MA holders with products authorized according to the decentralized procedure or the mutual recognition procedure, an authorized 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 approval stage, including the conduct of a
pre-marketing inspection of the MA holder's pharmacovigilance system according to the criteria for the feasibility of conducting the pre-marketing inspection in accordance with paragraph 4.2.1.3 of these Rules.

4.1.4. 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 of a particular medicinal product.

4.1.5. Authorized authorities of the Member States 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.

4.1.6. The inspection results shall be made available to the inspected party, which is allowed to comment in case of non-compliance with the requirements of the legislation of a Member State and these Rules. The MA holder must promptly eliminate the identified discrepancy by developing and implementing a corrective and preventive action plan.

4.1.7. If the inspection reveals that a MA holder does not comply with the pharmacovigilance obligations, the Member State's authorized authority must inform other Member States' authorized authorities about the violation detected. If necessary, the Member State's authorized authority should 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 authorized authorities of the Member States in the information and telecommunications network “Internet.”
4.2. Structures and Processes

4.2.1. Inspection Types.

4.2.1.1. Inspection of the pharmacovigilance system as a whole and for individual medicinal products.

4.2.1.1.1. 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 operation of the pharmacovigilance system.

4.2.1.1.2. Inspections aimed at assessing the performance of pharmacovigilance functions for a specific medicinal product include assessing and analyzing activities and documentation related to the specified medicinal product. Certain aspects 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 related to the medicinal product.

4.2.1.2. Scheduled and unscheduled pharmacovigilance system inspections.

4.2.1.2.1. 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, it is recommended to use an approach based on assessing the potential risks of non-compliance with the relevant obligations. Scheduled inspections are systemic inspections, but one or more specific medicinal products can be selected as examples to check the functioning of the pharmacovigilance system and obtain experimental evidence of its effective
functioning and compliance with the requirements of the legislation of a Member State, international treaties, and acts that constitute the right of the Union. A routine inspection program could, for example, include an assessment of the state of the system for specific problems identified by experts.

4.2.1.2.2. 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 performed when one or more of the following triggering factors are identified.

4.2.1.2.2.1. Factors in terms of the risk-benefit ratio for a medicinal product:

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.

Presentation of information on the problems of pharmacovigilance in the media without prior or simultaneous notification of authorized authorities of the Member States.

Non-compliance with the requirements of the legislation of a Member State, international treaties, and acts constituting the right of the Union, or obligations to ensure the safety of a medicinal product, revealed during the
pharmacovigilance activities monitoring by the Member States' authorized authorities.

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

4.2.1.2.2.2. Factors in terms of reporting obligations (urgent and periodic):

Delay or omission in the submission of safety information in accordance with the requirements of the legislation of a Member State, international treaties, and acts constituting the right of the Union.

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.

4.2.1.2.2.3. Factors in terms of requests from the authorized authorities of the Member States:

Refusal to submit the requested information within the time frame specified by the Member States' authorized authorities.

Poor quality of the data submitted or their inadequate submission upon requests from the Member States' authorized authorities for the provision of information.

4.2.1.2.2.4. Factors in terms of fulfilling the established obligations:

Concern (reasoned opinion regarding the lack of organizational 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 examination procedure of the Drug Master File.

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

4.2.1.2.2.5. Factors in Terms of Inspection:

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

Obtaining, when performing other inspections for compliance with the requirements of Good Pharmaceutical Practices, information on non-compliance with the requirements of the legislation of a Member State, international treaties, and acts constituting the right of the Union, or obligations to ensure the safety of a medicinal product.

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

4.2.1.2.2.6. Other factors:

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.

4.2.1.3. Pre-marketing inspections.

4.2.1.3.1. Pre-marketing pharmacovigilance system inspections are carried out before the issuance of marketing authorization to the applicant. The purpose of such inspections is to examine a functioning or planned pharmacovigilance system following the applicant's description of the system. Pre-marketing pharmacovigilance system inspections are optional but
may be required under certain circumstances. The principles for requesting a pre-marketing inspection should be determined in advance and should not give rise to unreasonable inspections that could delay the issuance of the marketing authorization. The following factors should be taken into account when considering the feasibility and reasonableness of performing pre-marketing 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' authorized 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-marketing inspection of the pharmacovigilance system may be one of the mechanisms to confirm that the system has been appropriately corrected or improved.

In the presence of problems regarding the safety of certain medicinal products, it may be considered necessary to assess the possibilities on the part of the MA holder:

Implementation of risk minimization measures associated with a specific medicinal product.

The proper fulfillment of special requirements to ensure the safety of the use of medicinal products that may be established.

The proper performance of routine pharmacovigilance procedures for the medicinal product with safety concerns.
Decision-making on the implementation of a pre-marketing inspection includes a risk assessment with a comprehensive assessment of issues related to certain medicinal products and the system.

4.2.1.3.2. If, as a result of the pre-marketing inspection of the pharmacovigilance system, concerns arise 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 authorized authority of a Member State may take the following measures:

a. Refusal in the issuance of marketing authorization, non-confirmation of approval (renewal), or other approval procedures.

b. Performing a re-inspection before the issuance of marketing authorization to confirm the elimination of critical inconsistencies and the implementation of recommendations.

c. Issuance of marketing authorization with a recommendation to inspect the pharmacovigilance system at an early post-marketing stage. The limitation of the period of time when a re-inspection is included in the plan for conducting scheduled inspections 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 authorization.

4.2.1.4. Post-marketing inspections.

Post-marketing pharmacovigilance system inspections are carried out after getting marketing authorization and are designed to assess the fulfillment of the MA holder's pharmacovigilance obligations. Post-authorization inspections can be of any type in accordance with paragraphs 4.2.1.1 and 4.2.1.2 of these Rules.

4.2.1.5. Announced and Unannounced Inspections.
Most pharmacovigilance system inspections will be announced, which entails notifying the inspected party to ensure that appropriate persons are present 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 on a tight schedule for urgent safety reasons).

4.2.1.6. Re-Inspections.

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.

4.2.1.7. Remote Inspections.

Inspectors carry out remote pharmacovigilance system inspections without visiting a MA holder or the organization to which the pharmacovigilance functions are delegated. These inspections can be carried out using the information and telecommunications network “Internet” 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 in case of 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 authorized 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.

4.2.2. Inspection Planning.

4.2.2.1. The planning of pharmacovigilance system inspections should 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.

4.2.2.2. Pharmacovigilance system inspection plans are drawn up by the Member States' authorized 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:

   Approval of a medicinal product for which additional pharmacovigilance activities or additional risk minimization measures are prescribed.

   Approval of a medicinal product for which post-authorization safety studies or additional monitoring are prescribed.
Approval and delivery of a medicinal product with a large sales volume, i.e., with a potentially significant impact on large patient populations.

Approval of a medicinal product that has no alternative on a Member State's market.

c. Factors associated with a MA holder:
   a MA holder whose pharmacovigilance system has never inspected.
   a MA holder keeping a significant number of medicines in circulation in the markets of the Member States.
   a MA holder who previously did not get marketing authorization in the territories of the Member States.

Negative information regarding the fulfillment of mandatory requirements and (or) in connection with the emergence of problems on the safety of medicinal products received from the Member States' authorized authorities and other countries carrying out pharmacovigilance, as well as from authorized authorities in other areas of regulation of the circulation of medicinal products (i.e., relevant Good Pharmaceutical Practices).

Changes in the organizational structure of a MA holder, such as mergers and acquisitions.

d. Factors associated with a pharmacovigilance system:
   a MA holder who has a subcontractor to carry out pharmacovigilance activities (in terms of the functions of a pharmacovigilance officer, safety data submission, etc.) and (or) several organizations involved in carrying out pharmacovigilance activities.

   Replacement of the 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.

Delegation or transfer of management of the pharmacovigilance system master file.

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

4.2.2.3. Authorized 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.

4.2.3. Inspected Sites.

Any party that carries out pharmacovigilance activities in whole or in part 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 can be located on the territory of the Member States or outside of them. Inspections of sites outside the Union can be carried out if the main pharmacovigilance center, databases, and (or) performed pharmacovigilance activities are outside the Union. The type and number of inspected sites must be selected appropriately to ensure that the inspection's key objectives are met.

4.2.4. Inspection Scope.

Inspection scope depends on inspection objectives, the coverage of previous inspections by the Member States' authorized 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, for example, data on the system's compliance to the Member State's authorized authority.

c. Specific factors for initiating an inspection in accordance with paragraph 4.2.1.2. of these Rules.

4.2.4.1. Standard Pharmacovigilance Inspections.

In the process of conducting standard pharmacovigilance system inspections, inspectors check compliance with the requirements of the legislation of a Member State, international treaties, and acts constituting the right of the Union concerning pharmacovigilance. If applicable, the inspection should 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 organizations within the pharmacovigilance system, including from those organizations that, on a contractual basis, fulfill a MA holder's pharmacovigilance obligations as well as from other organizational units not related to the pharmacovigilance system.

   Evaluation of reports, including mechanisms for receiving and registration procedure, evaluation of reporters, the terminology used, evaluation of severity, 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).

   Fulfillment of the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union on the submission of various types of individual case safety reports for a medicinal product to the Member States' relevant authorized 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, presentation of relevant analyzes and measures.
Registration and presentation of information in a periodic safety update report in accordance with the established requirements.
Timeliness of 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' authorized 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 appeals to healthcare workers and patients.

d. Interventional (if necessary) and non-interventional clinical studies:
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 studies.

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:

Roles and responsibilities of a pharmacovigilance officer, 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 legislation of the Member States, international treaties, and acts constituting the right of the Union.

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 computerized systems used to perform specific functions.

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

An inspection may include assessing compliance with the terms of approval and compliance of the implemented risk minimization measures with established requirements.

4.2.4.2. Unscheduled Inspections.

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 4.2.4.1 of these Rules, as well as the following:

a. Involvement and awareness of a 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.

4.2.4.3. Re-Inspections.

4.2.4.3.1. 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 a 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.

4.2.4.3.2. 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, if applicable).

4.2.5. Inspection Process.

4.2.5.1. 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 harmonization of inspections will be facilitated by agreed processes and procedures, joint inspections, exchange of experience, and training of the inspectorates of the Member States' authorized authorities.

4.2.5.2. Pharmacovigilance system inspection procedures should include the following processes:

a. Exchange of information.

b. Inspection planning.

c. Pre-marketing 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) Recommendations for the training of inspectors performing pharmacovigilance system inspections and the experience exchange.

4.2.5.3. Development of new procedures is possible if necessary.

4.2.6. Monitoring the implementation of inspection remarks.

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 controls should be considered:

a. Analysis of the of a 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 implement appropriate information sharing, including introducing changes to the information provided within marketing activities and (or) advertising information.

f. 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 authorized 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 authorization or clinical study approval).

4.2.7. Actions and Sanctions of authorized authorities of the Member States.

4.2.7.1. Authorized authorities of the Member States 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 should be determined on a case-by-case basis. What action to take should depend on the potential negative impact of non-compliance (inconsistencies) on public health, but any case of non-compliance (inconsistencies) can be taken into account when applying enforcement measures. If necessary, the Member State's authorized authority should ensure that effective, proportionate, and deterrent measures are applied to a MA holder.

4.2.7.2. In accordance with these Rules and, if necessary, with the rules established by the legislation of the Member States, in case of non-
compliance with pharmacovigilance obligations, the following Rules options are possible:

a. Training and assistance: authorized authorities of the Member States have the right to 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 authorized authority, and consider corrective and preventive actions proposed by the MA holder.

b. Submission of information to other authorized 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 (non-compliance) with the legislation of the Member States, international treaties, and acts constituting the right of the Union, and subsequently to confirm their compliance.

d. A warning letter, statement of non-compliance, or notification of a violation, issued by the Member State's authorized 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 must accept, as well as on the deadlines set for the elimination of inconsistencies or violations.

e. Consideration by the Member States' authorized authorities of publishing the list of MA holders who seriously or constantly violate the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union.

f. Actions regarding the Drug Master File or marketing authorization application of a medicinal product, for example:

Urgent introduction of restrictions related to the safety profile of a medicinal product.
Suspension or cancellation of the marketing authorization of a medicinal product.

Suspension of consideration of new applications for obtaining marketing authorization until the corrective and preventive actions are implemented.

Appointment of pre-marketing pharmacovigilance system inspections.

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. Amendments to protocols or suspension of clinical studies 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.

4.2.8. Qualification and training of inspectors.

Inspectors who conduct pharmacovigilance system inspections must be specialists from the Member States' authorized authorities or persons appointed in accordance with the requirements of the legislation of the Member State and must also comply with the provisions of the quality manual for the inspectorate of the Member State's authorized authority. It is recommended that inspectors' designation be based on their experience and the minimum requirements determined by the Member State's authorized authority. Inspectors should 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 should 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.

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

4.3. Cooperation within the Union

4.3.1. Sharing Information.

authorized authorities of the Member States must 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 scope of the inspection to plan further 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. authorized authorities of the Member States exchange information on critical and significant identified deficiencies and a summary of corrective and preventive actions and their further control.
4.4. Role of authorized authorities of the Member States

Authorized authorities of the Member States shall ensure the establishment of a legal and organizational basis for performing the functions of inspecting the pharmacovigilance systems of MA holders, including defining the rights of inspectors concerning the inspection of pharmacovigilance activities and the assessment of pharmacovigilance data.

The Member States should 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. Authorized authorities of the Member States may, if necessary, send a request for assistance in inspecting another authorized authority of the Member States with the provision of appropriate access to the inspection site and the evaluated data of the pharmacovigilance system.

Authorized authorities of the Member States should ensure the planning and conduct of pharmacovigilance system inspections of MA holders in accordance with paragraph 4.2 of these Rules.

When developing the inspection plan, the authorized authority of the Member State asks other authorized authorities of the 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 authorized authorities of the Member States to minimize unreasonable duplication of work performed and optimizing the use of available resources.
Suppose the Member State's authorized authority of plans to conduct an inspection of a MA holder who was inspected by another authorized authority of the Member State; in that case, the exchange of information regarding the scope and results of the performed inspection should be ensured to take into account the available data when planning, determining the scope and the time of the inspection.

It is recommended to form a single information resource, including the inspection results of MA holders' pharmacovigilance systems, with access to the Member States' authorized authorities.

4.5. Role of MA Holders

MA holders with medicinal products authorized in the Member States territories are subject to pharmacovigilance system inspections. MA holders are required to:

a) Always be ready for inspection, as inspections can be unannounced.

b) Conduct and present at the request of inspectors no later than 7 working days after receiving the corresponding request for the pharmacovigilance system master file.

c) Ensure that previous inspection consent is obtained for the conduct of an inspection from sites selected for inspection, which may include organizations 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.

d) Ensure that appropriate personnel involved in pharmacovigilance activities are present during the inspection and provide clarification on emerging issues.
e) Ensure the proper and timely implementation of corrective and preventive action plans to eliminate deficiencies (inconsistencies) identified during the inspection with prioritization of critical and significant deficiencies (inconsistencies).

4.6. Inspection Fees

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

5. Pharmacovigilance System Audit

5.1. Structures and Processes

5.1.1. Pharmacovigilance System Audit and Its Objectives.

5.1.1.1. 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.

5.1.1.2. 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 performance and control standards against which the auditee and its performance are assessed. Concerning the pharmacovigilance system, the audit criteria should 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.

5.1.2. Risk-Based Approach to Pharmacovigilance Audits.

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 severity of its consequences and (or) the likelihood of not being detected by other methods. The risk-based approach to audits focuses on the highest risk areas to the organization'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 recommendations.

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

5.1.2.1. Strategic Audit Planning.

5.1.2.1.1. An audit strategy is a definition at the highest level of planning for audit activities that are planned for a period of more than 1 year (usually for a period of 25 years). The audit strategy includes a list of audits that may be sufficient. The audit strategy is used to define 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.

5.1.2.1.2. An audit strategy should cover the organization of process management, risk management, and internal controls for all pharmacovigilance system components, including the following:
  a. All processes and tasks of the pharmacovigilance system.
  b. Quality system of pharmacovigilance activities.
  c. Interaction and liaisons with other departments (if necessary).
  d. Pharmacovigilance activities carried out by subordinate organizations or delegated to another organization (e.g., regional sites providing information, branches of a MA holder, third parties such as contractors and other MA holders).

5.1.2.1.3. Risk factors to consider when performing a risk assessment procedure include, but are not limited to:
  a. Changes in the legislation of the Member States on pharmacovigilance or these Rules.
  b. Major reorganization 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 taking into account the new requirements of the legislation of the Member States).
  f. The first medicinal product on the market (for MA holders).
g. Medicinal product on the market with additional risk minimization measures introduced or other circulation conditions related to the safety profile of products (e.g., the establishment of additional monitoring).

h. The degree of criticality of the process, in particular:

For the Member States' authorized authorities, how critical the area or process is about the proper functioning of the pharmacovigilance system of the Member States and the overall objectives of the health system.

For MA holders, how critical the area or process is about the pharmacovigilance system's proper functioning. When deciding to audit a branch or a third party, the MA holder must take into account the nature and criticality of the pharmacovigilance activities that are carried out currently by an affiliate or a third party on behalf of a MA holder, in addition to taking into account other factors included in this list;

i. Results of previous audits (whether this area or process has ever been audited, the results of a previous audit); if the results of previous audits are available, they are taken into account when determining the timing and scope of subsequent audits.

j. Identified procedural deficiencies (inconsistencies) related to specific areas of activity or processes.

k. Other information regarding the fulfillment of obligations in accordance with the requirements of pharmacovigilance legislation:

For the Member States' authorized authorities, information on compliance with the requirements assessed or audited by external organizations.

For MA holders, information on compliance with requirements according to inspection reports, assessments or audits performed by external organizations, complaints or grievances regarding pharmacovigilance obligations.
1. Other organizational 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).

5.1.2.2. Tactical audit planning.

5.1.2.2.1. An audit program is a list of audits consisting of one or more audits scheduled for a specific period, usually 1 year. The preparation of the audit program should be carried out in accordance with the long-term audit strategy. The audit program must be approved by top management with overall responsibility for the operational and management structure.

5.1.2.2.2. An audit program is based on a proper risk assessment and should focus on assessing the following:

a. Pharmacovigilance quality system.

b. Critical processes in the pharmacovigilance system.

c. Key control systems based on pharmacovigilance activities.

d. High-risk areas after implementation of control procedures and risk minimization measures.

5.1.2.2.3. A risk-based audit program should also take into account the results of previous audits in terms of insufficient coverage of activity areas, high-risk areas, as well as a direct designation of management and (or) persons who are responsible for the pharmacovigilance system.

5.1.2.2.4. An audit program documentation should 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 program should be based on a documented risk assessment. Risk-based pharmacovigilance system audits should be performed regularly in accordance with the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the
Union. Reasonable changes to the audit program should be properly documented.

5.1.2.3. Operational Audit Planning and Reporting.

5.1.2.3.1. Field Planning and Data Collection.

The organization shall implement procedures in written form, taking into account the planning and conduct of individual audits. The time frame for all measures required to complete an individual audit should be established in the relevant audit procedures. The organization shall ensure that audits are conducted following these procedures in accordance with this section.

Individual pharmacovigilance system audits should be carried out under the approved risk-based audit program in accordance with paragraph 5.1.2.2 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 method for performing the audit is appropriately documented in the audit plan.

5.1.2.3.2. Reporting.

Auditors' findings are documented in the auditor's report and reported to management on time. The audit process should include mechanisms for communicating the audit findings to the auditee, obtaining feedback, and submitting audit reports to management and stakeholders, including those responsible for the pharmacovigilance system, in accordance with the requirements of the legislation of the Member States, international treaties, and acts that constitute the right of the Union, and recommendations for the pharmacovigilance system audit. Audit results should 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. The classification system should be defined in the pharmacovigilance quality
system description and should take into account the following thresholds, which should 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 legislation of the Member States, international treaties, and acts constituting the right of the Union.

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 performed pharmacovigilance procedures, which adversely affects the entire process and (or) can potentially affect the rights, safety and the well-being of patients, and (or) may pose a potential threat to public health and (or) creates a violation of the requirements of the legislation of the Member States, international treaties, and acts constituting the right of the Union, which, however, 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 rights, safety, and well-being of patients.

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

5.1.2.4. Actions based on the results of the audit and the follow-up control of the audits.

5.1.2.4.1. 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 timing of actions associated with an identified critical deficiency (inconsistency) may vary depending on the nature of the findings and the planned action.

5.1.2.4.2 The organization's management ensures that the organization has a mechanism to resolve issues related to the pharmacovigilance system audit results properly. The set of measures should 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.

5.1.2.4.3. Top management and those charged with governance should ensure that all necessary and effective steps are taken to correct deficiencies identified during the audit. The implementation of the agreed actions should be systematically monitored. Information on the progress of implementing corrective and preventive actions should 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 should be properly documented. The audit program should include the potential for surveillance audits to be performed as needed to confirm that agreed actions have been completed.

5.1.3. Quality and Documentation System.

5.1.3.1. Competence of auditors and audit quality management.

5.1.3.1.1. Independence and objectivity of the audit and the work of auditors.
An organization should have specific responsibilities for pharmacovigilance audit activities. The activities for performing the pharmacovigilance system audits should be independent. The organization's management should ensure and document the independence and objectivity of the auditors.

Auditors should be free from interference in determining the audit scope, conducting a pharmacovigilance system audit, and communicating the audit results. Key reporting should be directed to top management, who has overall responsibility for the executive and management structure to enable the auditor to discharge his responsibilities and provide an independent and objective auditor's opinion. Auditors can consult with experts, personnel involved in pharmacovigilance processes, and a 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, should not take the point of view of the experts involved as a priority.

5.1.3.1.2. Qualification, professionalism, experience and continuing professional development of auditors.

Auditors should have the required qualifications and maintain them in terms of the knowledge, skills and abilities necessary to conduct and participate in effectively pharmacovigilance system audit activities. Auditors should 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. Organizational systems.
5.1.3.1.3. Assessment of the quality of audit activities.

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

5.1.3.2. Audits conducted by external audit service providers.

The primary responsibility for the functioning and effectiveness of the pharmacovigilance system rests with the organization. If the organization 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 organization shall communicate the requirements and preparation of the audit risk assessment, audit strategy, audit program, and individual audit engagements to the external service providers in writing.

b. The organization should communicate the scope of work, objectives, and procedural requirements for the audit to the external service providers in writing.

c. The organization shall obtain documentary evidence of the independence and objectivity of external audit service providers.

d. An external audit service provider must also comply with the relevant requirements given in these Rules.

5.1.3.3. Storing audit reports.

Audit reports and information confirming the completion of audit actions should be kept in accordance with the requirements specified in Section 2 of these Rules.

5.2. Audit Requirements
5.2.1. MA Holders.

5.2.1.1. Audit requirements.

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 should be properly documented.

5.2.1.1.1. Pharmacovigilance officer in the Member States.

A pharmacovigilance officer's responsibilities concerning audit activities are defined in Section 2 of these Rules. A pharmacovigilance officer in the Member States should 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 pharmacovigilance officer in the Member States should be informed of the results of any audit related to the pharmacovigilance system in the Member States, regardless of where it is carried out.

5.2.1.2. Authorized authorities of the Member States.

5.2.1.2.1. Audit requirements.

The Member State's authorized authority should 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 should be properly documented.

5.2.1.2.2. Methodology adopted.

To ensure a coordinated and harmonized planning and implementation of audits and the preparation of their reporting, audits carried out in the
Member States' authorized authorities should be based on the adopted terminology and methodology.

5.2.2. Requirements for audit reporting.

5.2.2.1. Reporting of a MA holder.

5.2.2.1.1. A MA holder must include an explanatory record of the pharmacovigilance system audit's critical and significant results in the pharmacovigilance system master file. Based on the audit results, the MA holder should 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.

5.2.2.1.2. A MA holder must 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 should be properly documented.

5.2.2.2. Reporting by authorized authorities of the Member States.

Authorized authorities of the Member States shall ensure that they ensure compliance with the reporting obligations on the audits performed in accordance with these Rules, international treaties, and acts constituting the right of the Union, and the legislation of the Member States, as well as the internal rules applicable to reporting.

5.2.3. Confidentiality.

The documents and information collected by the internal auditor should 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.

6. Risk Management System

6.1. Introduction

The risk management process consists of 3 interrelated and repetitive stages:

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).

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).

Planning and implementation of activities to minimize the consequences of risks and assess the effectiveness of these activities (risk minimization measures plan).

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

At the stage of getting marketing authorization for a medicinal product, as well as other stages of the life cycle, the necessary additional measures may be determined to study aspects of safety or efficacy or additional risk minimization measures to ensure the use of the medicinal product when the benefit exceeds the risk, which should be included in the risk management plan and executed by a MA holder.
Requirements for the format of data presentation in the risk management plan are defined in Annex 1 to the requirements for assessing the risk management plan.

6.2. Structures and Processes


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

The risk management plan is a dynamically changing document that must 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.

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

Important potential risks can be excluded from the safety specification of the risk management plan (e.g., in cases where the accumulated scientific and clinical data does not support the initial assumption about the degree of exposure to humans and the potential risk cannot be assessed as important; in cases where there is no reason to believe that any pharmacovigilance activity may further complement existing risk characterization data) or their
classification may be changed to include important identified risks (e.g., if scientific and clinical evidence strengthens the evidence base to support the relationship between risk and medicinal product).

Important identified risks may be excluded from the safety data sheet under certain circumstances, where it can be demonstrated that the risk is fully characterized and adequately managed (e.g., for drugs that have been used for a long time, for which at the current stage any additional pharmacovigilance activities and (or) recommended risk minimization measures have become fully integrated into standard clinical practice, for example, have been included in treatment protocols or clinical guidelines).

Considering the general objective to obtain more information on the risk-benefit ratio for certain populations not included in the pre-marketing study program for a medicinal product, relevant aspects of the missing information may be excluded from the section of the safety data sheet as safety data are obtained at the post-marketing stage, in cases where there is no reason to believe that pharmacovigilance methods currently available or in the future can complement existing risk characterization data concerning missing information.

Except for certain long-term patient registries, additional pharmacovigilance activities may be excluded from the risk management plan as they are implemented.

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

6.2.2. Responsibility for Risk Management within the Organization.

The main participants in the process directly involved in planning the risk management of medicinal products are the MA holders and the Member States' authorized authorities responsible for regulating the circulation of medicinal products.

6.2.2.1. MA holders.

Concerning the risk management process, a 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 must 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 should 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, an additional two stages below are recommended for revising the risk management plan for medicinal products approved according to the marketing authorization application on the initial submission of a complete dossier, reflecting the need
to amend the safety specification, as well as planned and ongoing pharmacovigilance activities and risk minimization measures:

Upon confirmation of approval (renewal) 5 years after getting marketing authorization.

During the submission of the first periodic safety update report after approval (renewal).

It is assumed that the submission of this periodic safety update report after approval (renewal) will be approximately 8 to 9 years after getting marketing authorization when the consideration of MA applications for generics with the corresponding active substance can begin. Therefore, it is assumed that the medicinal product's safety profile is likely to be sufficiently well characterized to allow a critical assessment and updating of the list of safety concerns.

6.2.2.2. Authorized authorities of the Member States.

Obligations of authorized authorities of the Member States to the risk management process are:

a. Continuous monitoring of the benefits and risks of medicinal products, 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 risk minimization measures associated with medicinal products and ensuring that the maximum possible benefit is obtained, including ensuring the accuracy and completeness of all information provided by MA holders concerning medicinal products.

c. Ensuring the implementation of risk minimization measures at the national level.

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 (if identified) by all MA holders concerning both original and generic, biosimilar medicinal products.

f. Provision of information to other authorized 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.

6.2.3. Risk Management Plan Objectives.

6.2.3.1. The risk management plan contains information that must meet the following requirements:

a. Determine and characterize the medicinal product's safety profile.

b. Indicate how the further characteristics of the safety profile of a medicinal product can be supplemented.

c. Documentary evidence of the adoption of measures to prevent or minimize the risks associated with using a medicinal product, including an assessment of the effectiveness of these measures.

d. Documentary confirmation of the fulfillment of post-marketing obligations to ensure the safety of use introduced during a medicinal product's approval.

6.2.3.2. To meet the requirements specified in paragraph 6.2.3.1 of these Rules, the information contained in the risk management plan must include:

a. Description of known and unknown information about the medicinal product's safety profile.

b. An indication of the degree of confidence that the effectiveness of a medicinal product demonstrated in the target populations during clinical
studies will be achieved in daily medical practice and documenting the possible need for efficacy studies in the post-marketing period.

c. An indication of the planned method for assessing the effectiveness of risk minimization measures.


The risk management plan consists of 7 parts. The submitted risk management plan must comply with the risk management plan template (Annex 1 to the Requirements for assessing the risk management plan).

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 document should be presented as a single document, including all modules and annexes in accordance with the relevant requirements of this section of the Rules.

The parts and modules of the risk management plan include the following:

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 Studies.
Module CIV: Populations Not Examined in Clinical Studies.
Module CV: Post-Marketing Experience.
Module CVII: Identified and Potential Risks.
Module CVIII: Summarized Safety Information.
Part III: Pharmacovigilance Plan.

Part IV: Plan for Post-marketing Efficacy Studies.


Part VI — Summary of the Risk Management Plan;

Part VII: Annexes.

The amount of information, especially in part II of the risk management plan, should 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.

The risk management plan for advanced therapy medicinal products should consider the special requirements determined for this group of drugs concerning support at the post-marketing 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 authorized authority before applying for marketing authorization 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-marketing monitoring of this group of pharmaceuticals' efficacy and safety, determined by the documents of the Union, should be taken into account.

If a 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).

Information in the risk management plan should be provided in sufficient detail; still, it is not allowed to include unnecessary text that is not directly relevant and distracts from the critical aspects of the information
presented, which must be taken into account for the formation of a risk management plan associated with the use of the product. The information in the risk management plan should provide 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-marketing data presented in other modules of the electronic common technical document. Any data included in the risk management plan should be consistent with the information provided elsewhere in the common technical document. The risk management plan should include references or links to the relevant sections of the preclinical and clinical reviews and summaries presented in the common technical document.

To ensure consistency between the information provided in the common technical document and the risk management plan, when presented as part of the common technical document, the following relationship between the information in the sections of the risk management plan and the modules of the common technical document should be considered:


Risk Management Plan: Part II, Module CI, Epidemiology of Indications by Target Populations—Common Technical Document: Module 2.5. Clinical Data Review;


Risk Management Plan: Part II, Module CIV, Populations Not Studied in Clinical Studies – Common Technical Document: Module 2.5 Clinical Data Review.


The data of the common technical document refers to cases of submission of a dossier included in the number of documents of the risk
management plan to get the marketing authorization (e.g., an application for initial approval or the introduction of significant changes), or refers to data previously submitted in the dossier.

Description of the content of the sections and modules of the risk management plan in accordance with paragraph 6.2.5 of these Rules in V.B.4 gives 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 this guide. Since the risk management plan is part of the medicinal product's scientific dossier, all information provided must be scientifically substantiated; it is not allowed to include elements of advertising information.

The section of the risk management plan preceding the main document should include the following administrative information:

Date of completion of data collection of the current risk management plan.

Date of signing and version number of the risk management plan.

List of all parts and modules. For updates to the risk management plan, this section should include in tabular form the version number of the modules and the date of approval (date of conclusion). 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.

Confirmation of the review and approval of the risk management plan by the 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 a pharmacovigilance officer. If the risk management
plan is submitted as part of the electronic CTD, as confirmation of control by the pharmacovigilance officer, a statement may be submitted that the risk management plan has been reviewed and approved by the pharmacovigilance officer of the MA holder and the document is certified with an electronic signature.

6.2.5. Detailed description of each part of the Risk Management Plan.

6.2.5.1. Risk Management Plan, Part I: Medicinal Product(s) Overview.

This part should 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 must be updated and accurately reflect the conditions for filing following the registration procedure performed.

The specified part should contain the following information:

a. Information about an active substance:

Active pharmaceutical ingredients (active ingredients) of the medicinal product(s).

Pharmacotherapeutic group (ATC Code).

Name of the MA holder.

When submitting under the decentralized procedure: the name of the planned MA holder in the Reference Member State.

Medicinal product for which this risk management plan has been developed (name and presentation).

Registration procedure (mutual recognition, decentralized, national).

Trade name in the Member States.

A summary of the medicinal product (including chemical class, a summary of the mode of action, important information about its composition (e.g., the origin of the active substance of biological medicinal products, appropriate adjuvants for vaccines)).
Reference to the section of the common technical document with information on the medicinal product, if applicable.

Indications (approved and proposed, if applicable).

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

Dosage forms and strength.

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


The purpose of this part is to provide a brief overview of the safety profile of a medicinal product, indicating the known safety information, as well as identifying the sections of the safety profile for which safety is not sufficiently studied. The safety data sheet should summarize the important identified risks of a medicinal product, important potential risks, and important missing information. The safety data sheet should 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-marketing 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 minimization plan.

The safety specification in terms of risk management includes 8 sections:

Module CI: Epidemiology of Indications for Target Populations.
Module CII: Preclinical Part.
Module CIII: Drug Exposure during Clinical Studies.
Module CIV: Populations Not Examined in Clinical Studies.
Module CV: Post-Marketing Experience.
Module CVII: Identified and Potential Risks.
Module CVIII: Summarized Safety Information.

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.

6.2.5.3. General recommendations for generic and advanced therapy medicinal products.

6.2.5.3.1. Generic medicinal products.

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 data sheet in force. If inconsistencies between the approved risk management plans for similar medicinal products, a MA holder must 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 current 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).

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

Due to their specific nature, advanced therapy medicinal products are characterized 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 must be taken into account when developing a safety specification for advanced therapy medicinal products.

6.2.5.2.1. Risk Management Plan, Module CI: Epidemiology of Indications for Target Populations.

The epidemiology of indications is the subject of description and assessment in this module. The description should include an estimate of the incidence rate, prevalence, mortality, data on untreated outcomes of the target population, the prevalence of co-morbidities in the target population; it should be presented with stratification by age, sex, and race, and (or) ethnicity if these population aspects are significant for safety assessment and risk management. Differences in epidemiology across regions should also be assessed and described (where regional differences are characteristic of epidemiology). If there are differences in the characteristics of the epidemiology of indications in the Member States territory, a description of these differences can be presented in Annex 9 to the risk management plan following the requirements for the format and structure of the data submitted. Information should also be provided on the risk factors for the disease and the main existing treatment approaches. The module includes information on adverse events expected (in the absence of treatment) in the target population, including the frequency and characteristics of adverse events. The data presented in the section should help predict and interpret potential signals and
determine the directions for minimizing risks. The information in the section should be short, accurate, and should not contain advertising elements.

6.2.5.2.2. Risk Management Plan, Module CII: Preclinical Part.

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

Toxicity studies (key data on toxicity obtained from studies, for example, acute and chronic toxicity, reproductive toxicity, embryotoxicity, teratogenicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity).

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

Data on drug interactions.

Other toxicity data.

The module should provide information on the significant toxic properties and the relevance of the findings when a product was used in humans. The data's significance is determined concerning the properties of the medicinal product, 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 significance of the obtained data on toxicity to humans. Besides, quality aspects should be discussed if they can significantly affect the medicinal product's safety profile (particularly, important information about the active substance 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. If preclinical (non-clinical) safety data may
represent an important potential risk to the target population, the relevant risk should be included as a safety concern in Module CVIII of the safety data sheet. Aspects of toxicity identified in preclinical (non-clinical) studies assessed as not significant in human use should be appropriately justified for the assessment performed and should not be included as safety concerns in Modules CVII and CVIII.

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

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

This section's content should be assessed in terms of consistency with the updated level of knowledge of the medicinal product throughout the product life cycle. At the post-marketing 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 identified 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-marketing stage or the generated evidence base, can be excluded from the list of safety concerns.

6.2.5.2.3. Risk Management Plan, Module CIII: Drug Exposure in Clinical Studies.

To assess the limitations of safety data obtained from studies with human participation, the module should provide data on patients included in
clinical studies (in which patient groups the product was studied). The data should be presented in a format suitable for analysis, for example, in the form of tables or graphs. Data for clinical studies are reported at the time of the initial submission of the risk management plan or significant changes to the section due to the update of data on impact assessment during clinical studies (e.g., for new indications). This section's content should be assessed for compliance throughout the product life cycle; in the absence of new significant data on the medicinal product's effects during clinical studies, updating of this section is not required.

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

- Age and gender.
- Indications.
- Strength.

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

If necessary, information on the study of the impact on certain populations (pregnant women, breastfeeding mothers, patients with renal failure, liver failure, cardiovascular disorders, subgroups of the population with the corresponding genetic polymorphism) should be provided. The severity of the impairment of renal, liver, or cardiovascular function, and genetic polymorphism, should also be indicated.

When reporting age data, categories that are relevant to the target population should be selected. Data for pediatric and elderly patients should
be separated according to accepted age categories (e.g., 65 to 74, 75 to 84, and over 85 for elderly patients). Final results should be presented at the end of each table or chart (as required).

Except where necessary, data on clinical studies should be presented summarized, not for individual clinical studies, 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 should be given.

If a risk management plan is submitted together with an application for a new indication, new dosage form, or route of administration, the details of the change should be presented separately at the beginning of this module and in the summary tables.

6.2.5.2.4. Risk Management Plan, Module CIV: Populations Not Studied in Clinical Studies.

This module of the safety specification is intended to describe populations that are considered in the context of missing information. This module should 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 studies (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 analyzed in clinical studies). 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 studies. Clinical studies' limitations should 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 versus general practice). Conclusions about the predictability of safety for target populations should be based on an accurate and detailed assessment of the limitations of available clinical study data, or lack thereof for any subgroup.

Suppose post-marketing use of a medicinal product is expected in populations that have not been studied in clinical studies 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, use in these unstudied populations should be included in the risk management plan as missing information. Populations excluded from the clinical development program should 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. In determining differences between target populations and populations that were included in a clinical study, it should be noted that specific differences may arise due to differences in the location of the study (e.g., hospital or general practice) and not due to particular inclusion or non-inclusion criteria. If it is proposed to attribute population data to missing information, the rationale for the relevant subpopulation should be included in Module CIV of the Risk Management Plan.
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 studies, this risk should be included in the list of important (potential) risks.

6.2.5.2.5. Risk Management Plan, Module CV: Post-Marketing Experience.

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

The section should include information reflecting the assessment of the use of a medicinal product in practice 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, assessment of use in special populations indicated in Module CIV.

The section should provide summarized data on the use of a medicinal product in third countries for indications not approved in the territory of the Member States, if applicable and relevant in the context of Module CVII, and the impact of these aspects on the use in the Member States should be assessed.


The section should provide an assessment of the potential for the risk of misuse of a medicinal product for illegal purposes and, if applicable, suggest risk minimization measures, for example, reducing the size of the package, introducing a controlled access program, and special requirements for the prescription of the product.
6.2.5.2.7. Risk Management Plan, Module CVII. “Identified and Potential Risks.”

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

Regarding the following aspects of the safety profile, a special assessment is required for the determination of the risks of a medicinal product, with the presentation of this assessment in the section if this risk is established:

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 characterized 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 studies, an appropriate indication should be made in the risk description, if necessary, important risks due to overdose should be included as safety concerns in Module CVIII of the safety specification with the proposal of appropriate risk minimization measures in Part V of the risk management plan;

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 studies at the stage of medicinal product development, medication errors were identified that led to important risks, the section 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. The assessment, presentation in the risk management plan, and the subsequent organization of work with medication errors should be based on the
recommendations on appropriate approaches to minimize the risk and prevent these errors, approved by the Commission. If at the post-marketing stage important risks associated with errors in the use of a medicinal product are identified, a risk assessment should be presented in the update of the risk management plan and measures to minimize medication errors should be proposed.

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.

The potential risk of out-of-specification use in cases where a difference in safety concerns is expected between the target populations 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 should be considered for inclusion in the safety data sheet.

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;

The important risks associated with the identified and potential pharmacokinetic and pharmacodynamic drug interactions should 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 summarized data confirming the interaction and the possible mode of interaction, the possible risks to patients'
health when used for various indications and in different populations, and plans for the further characterization and minimization of the described risks. Significant risks arising from interactions should be included in safety concerns;

Risks in pregnant and breastfeeding women (e.g., teratogenic risk) – direct or indirect through exposure to semen: contraceptive recommendations can be considered risk minimization measures.

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.

Risks associated with the disposal of the used product (e.g., transdermal patches with the residual active substance or residual amounts of radioactive diagnostic agents).

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).

Pediatric safety aspects considered as a safety concern for the pediatric population.

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, authorized authority has the right to request to supplement the section with an assessment of these risks.

Concerning the risk management plan for advanced therapy medicinal products, the development of safety specifications should consider risks specific to this drug group.
6.2.5.2.7.1. Risk Management Plan, Module CVII. “Safety Concerns Identified for a Medicinal Product during the Initial Risk Management Plan Submission.”

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

6.2.5.2.7.2. Risk Management Plan, Module CVII. “Risks Rated as Important for Inclusion in Safety Concerns” and “Risks Not Rated as Important for Inclusion in Safety Concerns.”

This section should provide information characterizing risk severity, frequency, and impact on the risk-benefit ratio.

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.

6.2.5.2.7.3. Risk Management Plan, Module CVII. “New Safety Concerns and Reclassification of Safety Concerns in Risk Management Plan Update.”

According to the safety data obtained at the post-marketing stage, information on new identified and potential risks is included in the documents and sections of the safety dossier (e.g., assessment of signals, periodic assessment of the risk-benefit ratio, 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 significant identified or potential risks should be reflected in Section 6.2.5.2.7.4. of the Risk Management Plan, “Details of Significant Identified and Significant Potential Risks.”

If a change in the classification assignment or exclusion from the list of safety concerns of important identified or important potential risks in this section, it is necessary to justify with an appropriate reference to the safety data. The information in this part of the requirements may be a statement describing a prior regulatory request, referred to the procedure, if such a request was made.

6.2.5.2.7.4. Risk Management Plan, Module CVII. “Details of Critical Identified, Critical Potential Risks, and Critical Missing Information.”

Concerning the risk management plan for combination drugs, where there are significant differences between the drugs (e.g., fixed doses in the form of combination drugs), it is necessary to clearly state which safety concerns relate to which of the pharmaceuticals in the combination.

This section of the risk management plan applies to all stages of the product life cycle.

The reporting of significant identified and significant potential risks should include the following details:

Risk name (using MedDRA terminology where applicable).

Potential mode of action.

Source of evidence and degree of evidence (i.e. scientific basis for suggesting a relationship).

Risk profile: that is, frequency, absolute risk, relative risk, severity, severity, reversibility, long-term outcomes, impact on life quality.

Risk factors and risk groups (including patient-related factors, dose, risk period, additive or synergistic factors).
Preventability (that is, the predictability of the risk; the presence of established risk factors that can be minimized through routine or additional risk minimization 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 severity of the adverse reaction.

Public health impact (e.g., the absolute risk concerning the size of the target population and, accordingly, the actual number of adversely affected persons, or the overall impact on the general population).

The submission of information on missing data should include the following:

Name of missing information (using MedDRA terminology where applicable).

Justification of the assumption that the safety profile in terms of missing information is different from the general target population.

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.

6.2.5.2.8. Risk Management Plan, Module CVIII: Summarized Safety Information.

The module provides summarized information on the identified safety concerns, which are classified into the following categories:

a. Significant identified risk.
b. Important potential risk.
c. Important missing information.


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 to:

- Studying the potential risk with the aim of confirming it as an identified risk or excluding it from the list of safety concerns.
- Further characterization of safety concerns, including severity, frequency, and risk factors.
- Determining methods for obtaining important missing information.
- Evaluating the effectiveness of risk minimization measures.

The pharmacovigilance plan should not include activities reducing, preventing, or managing risks; these activities should be presented in Part V of the Risk Management Plan.

The pharmacovigilance plan should focus on the safety concerns summarized in Module CVIII of the Safety Data Sheet of the Risk Management Plan and should be comparable with the medicinal product's benefits and risks. In case of doubt, it is recommended to carry out preliminary consultations of MA holders with the Member State's authorized authority as part of the scientific consultation procedure regarding the need and types of additional pharmacovigilance activities, the main stages, and timing of their implementation.

Pharmacovigilance activities are subdivided into routine pharmacovigilance activities and additional pharmacovigilance activities.

6.2.5.3.1. Risk Management Plan, Part III. “Routine Pharmacovigilance Activities.”

Routine pharmacovigilance activities are a set of basic activities that must be regularly performed by a MA holder for all medicinal products to ensure compliance with the requirements of the pharmacovigilance legislation of the Member States. 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 system of MA holders; there is no need to duplicate this information in the risk management plan.

The Member State's authorized authority has the right to recommend a MA holder to supplement the current procedures for collecting, verifying, evaluating, and submitting information on adverse reactions carried out within the framework of spontaneous reporting. Suppose this recommendation is limited to collecting additional structured data based on the assessment results of the patient's condition who has developed an adverse reaction performed as part of routine clinical practice; in that case, this activity will be considered routine. In this case, in this section, the MA holder explains the changes in routine pharmacovigilance activities introduced according to the proposals of the Member State's authorized authority.

In cases where the recommendation includes the submission of tissue or blood samples to a designated laboratory to assess additional parameters (e.g., determination of antibodies), which are not performed as part of routine clinical practice, this activity should be considered as an additional pharmacovigilance activity.

This section of the risk management plan should describe only routine pharmacovigilance activities beyond the activities performed to deal with adverse reaction reporting and signal detection.

6.2.5.3.1.1. Special Questionnaires for the Subsequent Collection of Information on Adverse Reactions.

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 these materials as part of routine pharmacovigilance activities and submit copies of these questionnaires to Annex 4 of 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.

Without compromising the originality of the questionnaire format, in the interest of public health, the questionnaire used by different MA holders for the same adverse event should be as similar as possible to provide consistent data for evaluation and regulatory decision-making while reducing the burden on health care professionals. Based on this, MA holders are strongly encouraged to provide available special questionnaires upon request to other MA holders.

6.2.5.3.1.2. Other Routine Pharmacovigilance Activities.

This section should include a description of other routine pharmacovigilance activities, for example, an enhanced passive monitoring program, analysis of observed versus expected data, cumulative reviews of adverse events of particular interest.

6.2.5.3.2. Risk Management Plan, Part III. “Additional Pharmacovigilance Activities.”

In this section, a MA holder describes the planned additional pharmacovigilance activities, specifying what information should 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.

Additional pharmacovigilance activities include pharmacovigilance activities that are not routine. This activity includes preclinical, clinical, and
non-interventional studies. Examples of such studies are a long-term follow-up of clinical study subjects or a long-term safety cohort study of a medicinal product. 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 authorized authority within the framework of the scientific consultation procedure.

Studies in a pharmacovigilance plan should focus on identifying and characterizing risks, collecting additional data on aspects of missing information, or evaluating the effectiveness of additional risk minimization measures.

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 authorized authority. The review and approved study protocols for the pharmacovigilance plan should be provided in Annex 3 (Part B) of the Risk Management Plan (or via electronic referencing or links to a protocol included in another section of the electronic CTD). Other Category 3 study protocols, provided for information only, may also be included in Annex 3 of the Risk Management Plan. After submitting the final report on the study results for assessment to an authorized authority, the protocols of completed studies are subject to exclusion from Annex 3 of the Risk Management Plan, and studies are excluded from the pharmacovigilance plan.

MA holders can submit to the Member States' authorized authorities the protocols of post-authorization safety studies for obtaining scientific advice.

6.2.5.3.3. Risk Management Plan, Part III. “Summary Table of Additional Pharmacovigilance Activities.”

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 a requirement for approval because they are either key to the risk-benefit ratio of a medicinal product (Category 1 studies in the pharmacovigilance plan) or certain obligations in the context of conditional approval under exceptional terms (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 authorized authority and, when planning and conducting the study, the MA holder must ensure that the requirements determined in Part VIII of these Rules are met.

In the risk management plan, other studies may be required to investigate the safety concern or evaluate risk minimization measures' effectiveness. Such studies included in the pharmacovigilance plan also have a legal basis (Category 3 studies in the pharmacovigilance plan). The summary table of the pharmacovigilance plan should provide clarity to all interested parties as to what pharmacovigilance activity category (registration condition, a certain obligation, or study is necessary to analyze a safety concern further or to assess the effectiveness of risk minimization 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 of the Eurasian Economic Union.

The risk management plan for generics should reflect the need to perform pharmacovigilance studies, if available at the time of approval. In certain cases, ongoing or planned post-authorization 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 prescribed treatment with a reference or generic medicinal product. Where applicable, joint post-authorization safety
studies are encouraged, for example, when introducing a register or determining the requirements for conducting this study for all authorized medicinal products with a specific active ingredient and used for a specific indication.


This section of the risk management plan should include a list of post-authorization efficacy studies with a specific obligation or condition for approval. If a MA holder does not have these obligations during marketing authorization, Part IV of the Risk Management Plan may be left blank.

6.2.5.5. Risk Management Plan, Part V: Risk Minimization Measures.

In accordance with the safety specification, the marketing authorization must assess what risk minimization measures are required for each safety concern. The risk minimization plan should include details of the risk minimization measures to mitigate the risks associated with each identified safety concern.

For similar active substances in separate different medicinal products with significantly different indications or target populations, it may be advisable to develop individual plans to minimize the risk specific to each of the products. That is, for medicinal products, the indications for the use of which relate to different fields of medicine and are associated with various safety concerns; for medicinal products that cause the different risks depending on the target population; for products with different prescription status, it is reasonable to develop individual risk minimization plans.

Risk minimization measures may consist of routine risk minimization measures and additional risk minimization measures. All risk minimization measures should have a clearly defined objective.
MA holders should periodically assess the need to continue implementing the established risk minimization measures and assess these measures' effectiveness. Guidance on additional risk minimization measures and assessing the effectiveness of risk minimization measures is provided in Part XII of the Risk Management Plan.

6.2.5.5.1. Risk Management Plan, Part V. “Routine Risk Minimization Measures.”

Routine risk minimization measures include activities (actions) that are carried out for each medicinal product. Routine measures cover:

- Summary of product characteristics.
- Labeling of a medicinal product.
- Package insert.
- 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 product's risk.

- Summary of product characteristics, package insert (leaflet).

Summary of product characteristics and package inserts are essential tools for minimizing risk since they represent a controlled and standardized format for sharing product-related information with medical and pharmaceutical workers and patients.

Summary of product characteristics and package inserts provide information on recommendations for routine risk minimization measures; this information includes two types of recommendations:

- Routine risk communication is based on the information included in Part 4.8 of Section 4 of the Summary of Product Characteristics and the package inserts, aimed at informing health care professionals and patients.
about the adverse effects of the medicinal product to decide on treatment considering the safety data;

Routine risk minimization 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 sections 4.1, 4.3, 4.5, 4.6, 4.7, and 4.9 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 the following:

- 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.
- Providing advice on contraception.
- Prohibition of the simultaneous use of other medicinal products.
- Impact on risk factors that can lead to an adverse event when using a medicinal product.
- Recommendations for long-term follow-up clinical observation for early detection of delayed adverse events.
- Packing size.

Planning the packaging size to limit the available number of medicinal product dosage units per one package is one of the routine risk minimization 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 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.

The prescription status of a medicinal product, which introduces control over its dispensing to the public, can help reduce the risks associated with its use or misuse. 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.

The marketing authorization 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. This is commonly referred to as the “prescription status” of a medicinal product. This status includes information about whether the product is prescription or over-the-counter medication. It can also restrict where it can be distributed (e.g., limiting its use in a hospital setting only). Concerning medicinal products that can only be purchased with a prescription, additional conditions must be introduced; namely, they must be classified into products that can only be purchased with a special prescription.

6.2.5.5.2. Risk Management Plan, Part V. “Additional Risk Minimization Measures.”

Additional risk minimization measures (that is, measures that do not belong to routine risk minimization measures) should be proposed when introducing additional measures is necessary to ensure the safe and effective use of the medicinal product. The need to continue additional activities should be reviewed periodically.
After their agreement with the Member States' authorized authority, additional risk minimization measures become a condition for obtaining a marketing authorization or maintaining authorization status. Where appropriate, full information on additional risk minimization measures should be presented in Annex 6 to the Risk Management Plan “Detailed Description of Additional Risk Minimization Measures.” Requirements and recommendations for additional risk minimization measures are defined in Section XII of the Risk Management Plan.

Evaluation of the effectiveness of risk minimization measures.

At the stages of updating the risk management plan, the risk minimization plan should include information on the estimated impact of the implemented additional risk minimization measures on the main parameters that determine these measures' effectiveness. Where applicable, this information should be provided concerning the Member States territories.

If applicable, the section should include a discussion of the results of any specific risk minimization assessment performed. If a particular risk minimization 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, a MA holder should consider alternative risk minimization measures. The MA holder should assess and comment in the risk management plan whether additional or other risk minimization measures need to be introduced for each safety concern or, based on the assessment performed, (additional) risk minimization measures may be excluded from the plan, for example, when risk minimization 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 minimization 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
product from the market or limit its use to only that patient subgroup for which the benefits outweigh the risks.

If the assessment of the effectiveness of risk minimization measures is a requirement or condition on the part of an authorized authority, these measures are included in the pharmacovigilance plan of Part III of the Risk Management Plan.

Recommendations for monitoring the effectiveness of risk minimization measures are included in Part XII of the Risk Management Plan.

6.2.5.5.3. Risk Minimization Plan Format.

In this section of the risk management plan, for each safety concern included in the safety specification, the following information on risk minimization measures should be provided:

Routine risk minimization 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 minimization measures are planned.

Additional risk minimization measures (if any), including tasks for each additional activity, the justification for the need, and a method for assessing additional risk minimization measures' effectiveness.

6.2.5.5.4. Risk Management Plan, Part V. “Summary of the Risk Minimization Plan.”

This section should provide a table listing the routine and additional risk minimization 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 minimization measures, or a list of educational materials).

A summary of the risk management plan for each medicinal product should be made publicly available. The executive summary should include the key elements of the risk management plan, with particular emphasis on risk minimization measures. Authorized authorities of the Member States should ensure that the summary of the approved risk management plans is published on the website.

The summary of the risk management plan should be promptly updated as important changes are made to the plan. Changes to the risk management plan are assessed as important if they affect:

- New significant identified or potential risks, important changes, or exceptions of the list of safety concerns.
- The inclusion or exclusion of additional risk minimization measures or routine risk minimization measures implementing specific clinical measures to risk management.
- Significant changes to the pharmacovigilance plan (e.g., adding new studies to the plan or completing ongoing studies).

Since the summary of the risk management plan is intended for a wide audience, the information in this section should be presented in understandable language. However, this does not mean that specialized terms should be avoided. The document should 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).

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 must contain the following information:
the medicinal product and for what purposes the use of the medicinal
product is approved
summary of safety concerns and missing information
routine and additional risk minimization measures
additional pharmacovigilance activities.


The risk management plan should include the following annexes, where applicable. If the risk management plan applies to more than one medicinal product, 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 emphasized (e.g., the form for the subsequent collection of information on an adverse event in Annex 4 may only apply to medicinal products containing an active substance that has a causal link to the event).

6.2.5.7.1. Annex 1 to the Risk Management Plan.

Annex 1 to the risk management plan is a structured electronic presentation of the risk management plan. It does not need to be submitted to eCTD; the electronic file must be submitted following the applicable guidelines. You can leave this annex blank.

6.2.5.7.2. Risk Management Plan, Annex 2: Brief Overview of Ongoing and Completed Pharmacovigilance Study Programs.

This annex should 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):

Planned and ongoing studies, including objectives, safety concerns, and planned timing for submitting intermediate and final results.
Studies completed, including objectives, safety concerns, and date of submission of results to authorized authorities (completed, planned submission, or indication of the reason for not submitting results).


Annex 3 is not required to include study protocols that have not been assigned by an authorized authority and are included in the pharmacovigilance plan. This annex may include an electronic reference or link to other modules of the eCTD dossier in the case of submission of these protocols to the eCTD and the submission of the risk management plan simultaneously with the eCTD. If the risk management plan is submitted outside of the eOPS, the annex should include the protocols of studies included in the pharmacovigilance plan.

6.2.5.7.3.1. Part A of Annex No. 3 to the Risk Management Plan. Requested pharmacovigilance study protocols submitted for assessment by an authorized authority when updating the risk management plan version.

If the requested protocols are to be submitted for consideration by an authorized authority and a MA holder plans to submit the study protocol for assessment by the authorized authority as part of the procedure for submitting a risk management plan, Part A must include this protocol. Alternatively, the study protocol can be reviewed in a separate procedure and, once agreed, should be included in Annex 3 (Part C) of the Risk Management Plan. The procedure for submitting the study protocol must be agreed upon with an authorized authority.

6.2.5.7.3.2. Risk Management Plan, Annex 3, Part B. Requested changes to previously approved pharmacovigilance study protocols submitted for assessment by an authorized authority when updating the risk management plan's version.
If the authorized authority has requested amendments 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 must include an updated protocol. Alternatively, an amendment to the protocol may be submitted under a separate procedure and, once agreed, should be included in Annex 3 (Part B) of the Risk Management Plan. The procedure for submitting the study protocol must be agreed upon with an authorized authority.

After approval by an authorized authority, the protocols from Part A or B should be transferred to Part C with a subsequent mandatory update of the risk management plan.

6.2.5.7.3.3. Risk Management Plan, Annex 3. Part B Approved protocols of performed pharmacovigilance studies and final study protocols not submitted for assessment by an authorized authority.

Previously agreed study protocols and final protocols not reviewed by the authorized authority should be included in Annex 3 (Part B) of the Risk Management Plan as follows:

Complete protocols that have previously been assessed by the authorized authority and agreed upon (i.e., no re-submission of the protocol has been requested). The protocols must be accompanied by the name of the procedure under which the protocol was approved and the conclusion date. The instruction might include an electronic submission or a link to other eCTD dossier modules if the protocols were previously submitted as part of the eCTD.

Final protocols for other Category 3 studies: Protocols that have not been requested for review by an authorized authority and are provided by the MA holder for information only.
Completed study protocols should be excluded from this annex after the final study reports are submitted to the authorized authority for evaluation.

6.2.5.7.4. Risk Management Plan, Annex 4: Special Forms for the Subsequent Collection of Information on Adverse Events.

This annex should include all forms of the subsequent collection of information on adverse events used by a MA holder to collect additional data on specific safety concerns. The use of the following forms included in this annex should be detailed in the pharmacovigilance plan in terms of risk management as a component of routine pharmacovigilance activities.

The forms of the subsequent data collection to be included in this annex may also be referred to as “questionnaires for additional adverse event data,” “adverse event data collection form,” or “form for the subsequent collection of adverse event data.”


This annex should include links or references to other parts of the eCTD dossier in the case of the inclusion of the efficacy study protocol in the eCTD or the protocol for the assigned efficacy study included in Part IV of the Risk Management Plan.


If applicable, this annex should include proposed drafts (and agreed, if applicable) of key information constituting additional risk minimization measures.

6.2.5.7.7. Risk Management Plan, Annex 7: Other Supporting Data (Including References).
If applicable, to avoid duplication of references, this annex should include eCTD references or links to other documents included in other dossier modules.


This annex should provide a chronological listing of all significant changes to the risk management plan. The information should include a summary of the changes, the date and version number of the risk management plan for all of the following changes:

- Adding, removing, or changing the classification of safety concerns.
- Adding or removing. Studies from the pharmacovigilance plan.
- Changing activities. In the risk management plan, in terms of measures that recommend certain clinical actions to manage risk or additional risk minimization measures.


This annex is submitted if information in the sections of the risk management plan in the Member States differs from the information in the corresponding sections of the current version of the risk management plan. A description of these differences in the risk management plan sections is presented following the data format and structure requirements.


The main post-marketing 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-marketing risk-benefit assessment; in contrast, the risk management plan's objective is
prospective pre-marketing and post-marketing risk-benefit ratio management and planning, so these documents are complementary.

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 significant 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 minimization plan should, 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.

In the following sections of the periodic safety update report and risk management plan, the information provided should be consistent but may differ in the format:


Part II, Module CV “Post-Marketing Stage” and Subsection 5.2 “Cumulative and Interval Exposure to Patients Based on Post-Marketing Experience” of the Risk Management Plan.


Subsection 16.5 “Risk Minimization Effectiveness” of the Periodic Safety Update Report.

6.2.7. Quality Systems and Records Management.

Although many experts may be involved in writing a risk management plan, the ultimate responsibility for its quality, accuracy, and scientific integrity rests with a 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 2 of these Rules. The MA holder must ensure control and documentation of the procedure for submitting the risk management plan to the Member States' authorized authorities, 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.

6.3. Requirements for Submission.

6.3.1. Requirements for the Risk Management Plan Submission for MA holders when Applying for Approval.

When applying for marketing authorization, alignment of a risk management plan with a description of the risk management system and a summary of the plan is provided for all medicinal products.

When applying to bring the Drug Master File to conformity with the requirements of the Union:

A medicinal product, the active substance of which has been well studied during medical use; in contrast, its efficacy and an acceptable degree of safety have been recognized, and at least 10 years have passed since the date of the first systematic and documented use of the active substance(s) of
herbal medicinal product, which meets the criteria for the simplified dossier submission.

A homeopathic medicinal product that meets the criteria for the simplified dossier submission.

A risk management plan is submitted only in the event of a new indication, in the event of a safety concern affecting the risk-benefit ratio of the medicinal product, or in other cases, when ensuring the use of a product when the benefit outweighs the risk requires the introduction of additional pharmacovigilance activities or risk minimization measures.

At the post-marketing period, the submission of an update to the risk management plan or a new risk management plan may be required at any time during a medicinal product's life cycle:

At the request of an authorized authority in the event of a safety concern affecting the risk-benefit ratio.

When making changes to the current Drug Master File, which are 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 minimization 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.

6.3.1.1. Requirements in Special Situations.

6.3.1.1.1. Applying for marketing authorization initially with the complete content of Modules 1 to 5 of the Drug Master File, it is necessary to submit all parts of the risk management plan. In all other cases of initial
submission for approval, the requirements for the content of the risk management plan are determined based on the concept of proportionality to the identified and potential risks of a medicinal product and the need to obtain safety data at the post-marketing period, in connection with which some parts or modules may be omitted if only the Member State's authorized authority does not provide other requirements. The minimum reporting requirements for the parts of the risk management plan are shown in Table 1.
Table 1

Summary of minimum requirements for the submission of information on parts of the risk management plan when initially applying for marketing authorization (a full description of the requirements is given in the text of the document)

<table>
<thead>
<tr>
<th>Medicinal Product Type</th>
<th>Part I</th>
<th>Part II</th>
<th>Parts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI</td>
<td>CII</td>
<td>CIII</td>
</tr>
<tr>
<td>Submission of the full content of Modules 1 to 5 of the Drug Master File</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Generic medicinal product</td>
<td>+</td>
<td>‡</td>
<td>+</td>
</tr>
<tr>
<td>Hybrid medicinal product</td>
<td>+</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Fixed combination medicinal products—with a new active ingredient in the composition</td>
<td>+</td>
<td>‡</td>
<td>‡</td>
</tr>
<tr>
<td>Fixed combination medicinal product—no new active ingredient in the composition</td>
<td>+</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Well-established use medicinal product</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Biosimilar medicinal product</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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 authorized authority.
3. The “*” symbol means that this section's information is provided if post-authorization 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 information on this section should be presented with an emphasis on the new active substance.
6.3.1.1.2. Submission for Approval of Generic Medicinal Products.

When applying for approval of generics, a risk management plan should be developed considering the following information requirements for sections:

Risk Management Plan, Part I: the information requirements for the section correspond to the requirements for this section, imposed in the case of submission for approval of the full content of Modules 1 to 5 of the Drug Master File.

Risk Management Plan, Part II: the information in the section should be presented, considering the following possible conditions.

The reference medicinal product has a risk management plan. In this case, the Modules CI to CVII of the risk management plan may not be submitted. Module CVIII should include summarized safety information generated from the summarized 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 defined in the risk management plan of the reference product, a detailed justification of the existing grounds for the changes and the corresponding safety concerns should be included in Module CVII. Likewise, if the MA holder has identified a new safety concern related to a generic drug (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 should 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 substance(s) of the product is published on the website of the Member State's authorized authority. In this case, when forming the safety specification, the requirements of the above paragraph are fulfilled. If more than one list of
safety concerns is published on the website of the Member State's authorized authority for a given active ingredient(s), the MA holder must justify the choice made in Module CVIII.

The reference medicinal product does not have a risk management plan; the list of safety concerns for the active substance(s) of the medicinal product is not published on the website of the Member State's authorized authority. In this case, during the safety specification formation, complete information on Modules CVII and CVIII is provided. Module CVII should 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 studies, scientific 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.

Risk Management Plan, Part III: the information should include a description of the pharmacovigilance activities in accordance with the requirements of 6.2.5.3. of these Rules.

A MA holder of the generic medicinal product is strongly encouraged 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-authorization safety studies, aimed at assessing the results of long-term use), which creates an unreasonable burden on patients, doctors and researchers and should be optimized through joint studies.
The Member State's authorized authority, where applicable, may also consider the prescription of studies to be carried out regarding generic medicinal products.

Risk Management Plan, Part IV: this part may be left blank if a post-authorization efficacy study has not been ordered for the generic medicinal product.

Risk Management Plan, Part V: if additional risk minimization measures are not taken for the reference medicinal product, in this part of the risk management plan, 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 original medicinal product. If new (other) risks associated with the use of a generic medicinal product are identified, Part V of the Risk Management Plan should provide risk minimization measures for the relevant safety concerns in accordance with the requirements established for this section when the full content of Modules 1 to 5 of the Drug Master File was initially submitted for approval.

If concerning the reference medicinal product, additional measures are taken to minimize risks, in Section V of the Risk Management Plan for the generic medicinal product, full information is required for the section in accordance with the requirements of paragraph 6.2.5.5. of these Rules.

Risk Management Plan, Part VI: the information in the section must comply with the requirements established for this section during the initial submission for approval of the full content of Modules 1 to 5 of the Drug Master File and be submitted in the data amount determined by the above requirements for the sections of the risk management plan of the generic medicinal product.
Risk Management Plan, Part VII: the information in the section must comply with the requirements established for this section during the initial submission for approval of the full content of Modules 1 to 5 of the Drug Master File. In terms of Annexes 4 and 5, a MA holder of the generic medicinal product is recommended to use the materials, the content of which has been brought in line with similar materials of the reference product.

6.3.1.1.3. Initial Submission for Approval of Hybrid Medicinal Products.

The information requirements in the sections of the risk management plan for hybrid medicinal products align with the requirements for generics following paragraph 6.3.1.1.2 of these Rules. In Part VII of the Risk Management Plan, a MA holder should provide a detailed assessment of the differences in the hybrid medicinal product compared with the reference medicinal product, for example, the active substance, 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. Data from clinical studies, which are the basis for submission for approval, should be included in Section II of the Risk Management Plan, Modules CI, CIII). Other parts of the risk management plan should also be brought in accordance with this information (e.g., Parts V and VI of the Risk Management Plan).

6.3.1.1.4. Submission for Approval of Fixed Combination Medicinal Products.

The information requirements in the sections of the risk management plan when applying for approval of fixed combinations are determined based on the following conditions:
In the case of a fixed combination medicinal product that contains a new active ingredient, the information in the sections of the risk management plan is determined by the requirements established for the initial submission for approval of the full content of Modules 1 to 5 of the Drug Master File. The information in the Modules CI to CVI of the Risk Management Plan should be presented with an emphasis on the new active ingredient.

In the case of a fixed combination medicinal product that does not contain a new active ingredient, the requirements for the sections of the risk management plan and information are determined by 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 authorized medicinal products containing similar active substances included in this fixed combination.”

New information obtained from the fixed combination study should be presented in Modules CII and CIII.

6.3.1.1.5. Submission for Approval of Well-Established Use Medicinal Products.

When applying for registration of well-established use medicinal products, a risk management plan should be developed considering the following information requirements for sections:

Risk Management Plan, Part I: the information requirements for the section correspond to the requirements for this section, imposed in the case of submission for approval of the full content of Modules 1 to 5 of the Drug Master File.

Risk Management Plan, Part II: the information in this section should be provided in Modules CVII and CVIII. A MA holder must provide a rationale for the proposed safety concerns or a rationale for the absence of
safety concerns based on the available data published in the medical literature.

Presented in case of submission for approval of the full content of Modules 1 to 5 of the Drug Master File.

Risk Management Plan, Parts III to IV: the information requirements for sections correspond to these sections' requirements if the full content of Modules 1 to 5 of the Drug Master File is submitted for approval.

6.3.1.1.6. Submission for Approval of Biological Medicinal Products.

When applying for approval of biological medicinal products, a risk management plan should be developed considering additional requirements for biological medicinal products, including:

Reflection of assessing the specific risk of immunogenicity with possible clinical consequences and the risk of transmission of infectious agents.

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-marketing use to the detection of the excess of the expected frequency, and measures to study specific risks at the post-marketing stage (e.g., immunogenicity).

Ensuring the inclusion in risk minimization measures of actions aimed to trace a biological medicinal product's name and batch during use and detecting adverse reactions.

6.3.1.1.7. Initial Submission for Approval of Homeopathic Medicinal Products and Herbal Medicinal Products That Do Not Meet the Criteria for Submitting a Simplified Dossier.
At the initial submission for approval of homeopathic medicinal products and herbal medicinal products that do not meet the criteria for submitting a simplified dossier, the information requirements for sections are determined based on the type of marketing authorization application.

6.3.2. Requirements for the First Submission of a Risk Management Plan after Approval.

6.3.2.1. Submission of New Risk Management Plans at the Request of the Member States' authorized authorities Connected with the Identified Safety Concern.

The requirements for the sections and information in the risk management plan submitted at the request of an authorized 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.

The Member State's authorized authority may determine the requirement for a MA holder to submit in Section CVII of the Safety Data Sheet regarding the identified safety concern or provide complete information on the medicinal product's safety concerns. The authorized authority makes this decision with the determination of the most optimal option in the current circumstances.


If a MA holder voluntarily submits a risk management plan after approval, the requirements for sections and information in the risk management plan are determined according to the type of approval of the medicinal product during the initial submission (e.g., approval with the submission of the full content of Modules 1 to 5 of the Drug Master File,
approval of a generic medicinal product, and so on) and the relevant requirements of paragraph 6.3.1 of these Rules.

6.3.3. Submission of the Risk Management Plan to the Member States' authorized authorities.

Upon initial submission for approval, the risk management plan must be submitted as part of the Drug Master File. When submitting a risk management plan as part of an electronic common technical document (eCTD), the document is generated in the form of PDF files or other electronic format determined by the requirements of authorized authorities of the Member States to the electronic format of marketing authorization documents following the approval procedure performed.

6.3.4. Risk Management Plan Updates.

If a MA holder has previously submitted the risk management plan during an approval procedure for an active substance, any subsequent submissions must be submitted as an update unless otherwise specified. Each submission of the risk management plan should be clearly versioned and dated. This refers to submitting the risk management plan in its entirety or only to a part or module of it. Revised versions that have identifying information must be submitted with a cover letter detailing the changes since the last version submitted.

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 minimization 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 minimization 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 minimization measures also cover excluding these additional measures from the risk management plan.

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 the routine activities to minimize risks, an update of the risk management plan may be required when supplementing the recommendations with certain specific clinical measures to manage the risk. For example, updating the risk management plan may also be warranted if there are significant changes in the annual expanded safety monitoring plan (routine pharmacovigilance activities), or if an additional component of routine monitoring, such as regular monitoring of renal function, is included as a recommendation in Section 4.4 of the Summary of Product Characteristics “Special Instructions and Precautions” (routine risk minimization activities). The need to update the plan for assessing the effectiveness of risk minimization measures should also be considered when updating the risk management plan.

An update to the risk management plan may be required upon completing an emergency safety issue assessment and confirmation of the new safety issue as an important identified or potential risk with the need to make changes to the safety concern list.

Unless otherwise specified by requirements, a document showing changes made to the most recent update to the risk management plan (if applicable) should be included with each update to the risk management plan.
that is submitted and changes from the currently approved version of the risk management plan.

A medicinal product can have only one currently approved version of the risk management plan. If there are differences in the information of the sections of the risk management plan (e.g., in terms of epidemiology, the stage of implementation of additional risk minimization measures, assessment of the risk minimization measures' effectiveness) in the Member States, a description of these differences in the sections of the risk management plan can be presented in Annex 9 in accordance with the requirements for the format and structure of the data presented. If multiple updates to the risk management plan are submitted during the procedure, the latest version submitted during the procedure will be considered the currently approved risk management plan for subsequent updates and tracking changes.

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.

At the post-marketing stage, the procedure for submitting a new or updated risk management plan outside of another regulatory procedure is regulated by the procedure for amending the Drug Master File.

6.3.5. Managing the Risk Management Plan When Executing Parallel Procedures.

If more than one procedure is performed simultaneously for a medicinal product that requires the risk management plan submission, it is recommended to submit a single combined risk management plan with the appropriate data division in Module CIII of the specified 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 should be discussed with an authorized authority before submitting the document.


If, when preparing a periodic safety update report, it is determined that it is necessary to amend the risk management plan as a result of identifying new safety concerns, or other data provided in the periodic safety update report, it is necessary to simultaneously submit the updated risk management plan to the Member State's authorized authority. In this case, a separate submission of the updated risk management plan is not required. Suppose the period for submission of both documents coincides, but the changes are not related to each other; in that case, the risk management plan submission should be considered a separate amendment and submission to an authorized authority of an updated version of the document.

6.3.7. Assessment of the Risk Management Plan by the Member States' authorized authorities.

For medicinal products authorized in accordance with the legislation of the Member States, the Member States' authorized authorities are responsible for evaluating the risk management plan. When organizing expert examination to assess the risk management plan, the Member States' authorized authorities use the guidelines for assessing the risk management plan adopted by the Commission. The Member State's authorized 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.
For medicinal products authorized under a decentralized procedure or recognition procedure, the risk minimization plan includes risk minimization measures recommended by a Reference Member State's authorized authority and subsequently agreed by the Member State's authorized authority. Additional risk minimization measures and other conditions or restrictions aimed at ensuring the use of a medicinal product when the benefit outweighs the risk are marketing authorization conditions.

authorized authorities of the Member States must ensure that MA holders containing the similar active substance(s) timely make changes to the risk minimization measures if there are changes about the reference medicinal product or a decision to amend the risk minimization measures for the active substance(s).

6.3.8. Transparency.

authorized authorities of the Member States 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.

authorized authorities of the Member States shall provide public access to the summary of approved risk management plans using the Internet portals of the Member States' authorized authorities.

7. Organization of Work with Information about Adverse Drug Reactions.

7.1. Structures and Processes

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 authorized in the Member States.
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 should be collected, analyzed, and presented in a periodic safety update report to interpret available safety data or assess the risk-benefit ratio.

7.1.1. Collecting Adverse Reaction Reports.

The Member States' authorized authorities and MA holders should take appropriate measures to collect and organize reports of suspected adverse reactions associated with the use of medicinal products obtained from various sources without prior request and received upon request.

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.

The system should be designed to provide an adequate assessment of the quality of the collected adverse reaction reports (in terms of authenticity, legibility, accuracy, consistency), the ability to perform validation, and the maximum completeness of clinical data evaluation.

Procedures for handling data in adverse reaction reports should be organized according to applicable data protection legislation of the Member States.

The system should be structured to allow for the timely validation of reports of suspected adverse reactions and their exchange with the Member States' authorities and MA holders within the time limits established by the legislation of the Member States.
Reports with safety information of a medicinal product collected at the post-marketing use stage can be divided into two types: reports received not upon request and reports received upon request.

7.1.1.1. Reports Not Received upon Request.

7.1.1.1.1. Spontaneous Reports.

A spontaneous report is a report that a healthcare professional, patient, or consumer sends to the Member State's authorized authority, MA holder, or another organization (e.g., regional site, poison control center) without prior request and that describes one or more suspected adverse reactions in a patient who has been prescribed one or more medicinal products. Spontaneous reporting does not include reports received in the course of study or other organized data collection types. Spontaneous reports also include the following adverse reaction reports:

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 organizations with their members' patients about pharmaceutical class action lawsuits.

Reports sent by consumers without prior request, regardless of subsequent medical confirmation.

Reports of suspected adverse reactions that are not associated with any of the organized data collection methods and received through the medicinal product information reporting system or result from the distribution of product information or educational materials.

Reports of suspected adverse reactions identified in the information and telecommunications network “Internet” or digital media.

Individual reports received from multiple reporters, with at least one sent without prior request.
Reports of suspected adverse reactions received during a non-interventional post-authorization study for which the study protocol did not determine a systematic data collection.

Reports of suspected adverse reactions resulting from compassionate use of unauthorized medicinal products or personalized programs for the use of unauthorized medicinal products if these programs did not determine the systematic collection of adverse reaction data.

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 should be included in the “Source” section of the adverse reaction report form.

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. If a consumer with medical training, including the patient himself, the patient's friend or relative, or caregiver, submits an adverse reaction report, this report is also assessed as having clinical confirmation.

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. The exception is reports in which the reporter has indicated no relationship between the adverse event and the intake of the suspected medicinal product.

7.1.1.1.2. Adverse Reaction Reports Published in the Medical Literature.

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 emergency safety issues. MA holders should be made aware of possible publications by performing a systematic literature review, widely used reference databases (including Medline or Embase) at least once a week. The MA holder should ensure that the literature review includes databases containing the maximum number of references to articles related to the medicinal product monitored. Besides, it should be ensured that all company representatives are aware of local medical publications and inform the company's safety department accordingly.

MA holders should review the reports of suspected adverse reactions published in the medical literature, including important published abstracts in conference proceedings or draft monographs, to identify and record reports of drug-related adverse reactions that are spontaneous reports or reports identified in the course of non-interventional post-authorization studies.

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.

Reports evaluated as valid shall be submitted to the Member States' authorized 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 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.

7.1.1.1.3. Reports from Other Sources.

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 should handle it as a spontaneous report. Every effort should be made to work through the case to obtain the minimum required information that constitutes a valid adverse reaction report. For this type of report, the time requirements for submitting reports apply, as for all spontaneous reports.

7.1.1.1.4. Information about Suspected Adverse Reactions from the Information and Telecommunications Network “Internet” or Digital Media.

MA holders should regularly browse the Internet or digital media on 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 a company if the MA holder owns, pays for, or controls them (and a donation (financial or otherwise) to an organization 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 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' authorized authorities is met, commencing the date the
information was posted. MA holders are encouraged to use their own websites to optimize the collection of suspected adverse reaction information.

Cases of suspected adverse reactions reported on the Internet or digital media received without request should be handled as spontaneous reports with reporting time requirements applied, as for other spontaneous reports.

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. If no information about the country of the source is available, then it should be the country where the information was obtained or where monitoring is carried out.

If the MA holder becomes aware of a suspected adverse reaction reported in digital media that the company does not sponsor, the report should be evaluated to determine if it is suitable for urgent reporting.

7.1.1.2. Adverse Reaction Reports Received upon Request.

Suspected adverse reaction reports received upon request are reports received from organized data collection systems that include clinical studies, non-interventional trials, registries, personalized programs of the use of unauthorized products, other programs of the use of such products in connection with exceptional circumstances of disease treatment and monitoring, interviewing patients or healthcare professionals or collecting patient data on the treatment efficacy or adherence. Adverse reaction reports received from any of these data collection systems should not be considered spontaneous reports except in the following cases:
Reports of suspected adverse reactions received during a non-interventional post-authorization study for which the study protocol did not determine a systematic data collection.

Reports of suspected adverse reactions resulting from the use of unauthorized medicinal products due to exceptional circumstances or personalized programs for the use of such products if these programs did not determine the systematic collection of data on adverse reactions.

As part of the reporting procedure, reports of adverse reactions received upon request should be classified as investigational reports, and validation and casualty assessment should be performed to ensure that they meet urgent reporting conditions.

Requirements for the organization of work with adverse reaction reports received upon request are included in paragraph 7.1.7.3 of these Rules.

7.1.2. Validation of Reports.

7.1.2.1. 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' authorized authorities must be validated for the minimum information required to fulfill this requirement. The minimum information required includes:

One or more identifiable reporter (source) who can be identified by attributes such as qualifications (e.g., doctor, pharmacist, another healthcare professional, patient, consumer, or other non-health professional), name, initials, or address (e.g., the name of the reporter's organization, street, city, state, postal code, country, email, telephone number). When organizing work with reporters' personal data, it must be ensured that the relevant legislation on the protection of personal data is complied with.
A reporter is considered identifiable if the organization from which an adverse reaction report was sent has reliable data to confirm this reporter's existence 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 organization informed of the case can prove it directly with the reporter. An individual case safety report will not be considered valid for submission to an authorized authority unless it contains the identification, qualifications, and country 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 source) in individual case safety reports, if applicable. 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.

An identifiable patient who can be identified by specifying at least one of the following characteristics: initials of the patient, number of the patient's medical record (document) (outpatient, inpatient card, examination card), date of birth, age, or age group, gestation period, and gender. A patient is considered identifiable if, based on the available data, it is possible to confirm the patient's existence. Patient identification information should be as complete as possible, taking into account the current local legislation on
personal data protection. A report can be considered valid for subsequent submission if at least one of the patient's above characteristics is present. 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 form a valid adverse reaction report.

One or more suspected medicinal products or active ingredients. Interacting drugs are suspected medicinal products.

One or more suspected adverse reactions. If the 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 Member State's authorized authority of 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 and 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 only contains information about the outcome and subsequent data collection does not provide a clinical rationale for identifying an adverse drug reaction as the cause of the resulting outcome, or the primary source does not indicate 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.
7.1.2.2. When collecting suspected adverse reaction reports via the information and telecommunications network “Internet” or digital media, the term “identifiable” refers to the ability to verify the existence of the reporter (source) and the patient.

7.1.2.3. The absence of any of these four minimum information elements means that the case is considered incomplete and is not subject to urgent adverse reaction reporting. Authorized authorities of Member States and MA holders should be cautious in collecting missing data elements in reports; actions for the subsequent data collection of adverse reaction reports should be documented. However, reports of adverse reactions for which minimal information is incomplete should be recorded within the pharmacovigilance system for use in ongoing safety assessment activities.

In the event of subsequent receipt of the minimum missing data on the adverse reaction report (including revision of the relationship of the adverse reaction with the intake of a medicinal product), the individual report is assessed as valid and must be reported in accordance with the requirements of these Rules.

7.1.2.4. If one party (an authorized authority of a Member State 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 should include all the important information necessary to detect a duplicate report.

7.1.2.5. If 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-marketing non-interventional studies, the case of an adverse reaction should not be relegated to a lower reliability category.
Adverse reaction reports should include the views of the investigator and MA holder or study sponsor.

7.1.2.6. A valid consumer adverse reaction report should not be categorized 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 originators.

7.1.2.7. If there is a disagreement between a reporter and a MA holder or authorized authority on assessing the adverse reaction as serious, the adverse reaction's severity should not be downgraded.

7.1.3. Follow-Up Work with Adverse Reaction Reports.

7.1.3.1. If, upon the initial receipt of a suspected adverse reaction report, the information is incomplete, follow-up work with such reports 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. Carrying out this work on the subsequent collection of information necessary for assessing an adverse reaction is especially important for monitored events of special interest, cases of exposure during pregnancy, cases of death of patients, cases involving the identification of a new risk or new aspects of a characteristic of a known risk. Actions for the subsequent collection of reported adverse reaction data and the resulting data should be documented.

7.1.3.2. In the absence of patient age information in an adverse reaction report, it is recommended that steps be taken to obtain data on the patient's age group or age due to the particular importance of evaluating safety information in specific age groups including pediatric and elderly patients.
7.1.3.3. 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 source (reporter) to submit new information that is important for the scientific assessment of the reported safety concerns. Using targeted, specialized questionnaires to collect additional important information about an adverse reaction avoids the need for the source to duplicate previously submitted data, makes it easier to complete, and helps optimize the important data collected for the evaluation. It is recommended that these targeted questionnaires be designed in a form that is as easy as possible to complete (e.g., using pre-filled fields where possible) and that the questionnaires be translated into the language used in the respective territory.

7.1.3.4. If information is obtained directly from a patient or consumer suspected of having an adverse reaction and is incomplete, attempts should be made to obtain consent to provide additional information from the appropriate healthcare professional. If a healthcare professional has confirmed (in whole or part) an adverse reaction for which the original report was submitted by a consumer or patient, this information should be accurately reflected in the individual case safety 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 about the medical confirmation of this case.

7.1.3.5. Regarding suspected adverse reactions associated with medicinal products of biological origin, accurate identification of the relevant medicinal product concerning its manufacture is of particular importance. Therefore, all appropriate measures should be taken to accurately indicate the medicinal product's trade name and the batch number of the medicinal
product. In the absence of data on the exact identification of a batch of a suspected biological medicinal product in the initial individual report, it is recommended to include an appropriate indication of the directed request in the description of the adverse reaction case. The response to the reporter's request for identification data for the batch of a suspected medicinal product is mandatory.

7.1.3.6. In certain cases, when it is not possible to collect information about an adverse reaction due to the anonymity of the reporter following local legislation on the protection of personal data, for example, in the 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 should be considered valid for submitting if the reporter's organization is capable of confirming the report directly with the reporter and the other minimum information criteria for the submitting are met.

7.1.4. Data management.

7.1.4.1. Electronic data and hard copy of suspected adverse reaction reports should be retained and handled in the same manner as other medical records (including meeting confidentiality requirements regarding patient and reporter identifiability), as required by the legislation of a Member State on personal data protection. Identifiable personal information about the reporting health care professional (reporter) should be kept confidential and protected from unauthorized access. The exchange of data between MA holders and authorized authorities regarding patients' and reporters' personal data should be organized, considering the requirements of the legislation of the Member State on personal data protection.

7.1.4.2. 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 authorized personnel. This 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.

7.1.4.3. If pharmacovigilance data transfers occur within an organization or between organizations, 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.

7.1.4.4. Storing data electronically must allow real-time access to the data by authorized persons.

7.1.4.5. The procedure for using specific terminology in data entry must be monitored and validated by performing a quality assurance audit systematically or by periodic sampling. Personnel must be instructed in data entry procedure using terminology, qualification of personnel must be periodically confirmed. Adverse reaction reports from the source (reporter) should be handled in an unbiased manner, without transforming the information or interfering with its text, and changes (adding or deleting information) should be avoided during data entry or electronic data transfer. Reports should include the verbatim text used in the source or an accurate translation. The original verbatim text should be reflected using appropriate terminology. To ensure the integrity of the information when encoding the report's text, it is recommended to use terminology in the local language or an accurate translation into English.

7.1.4.6. Electronic data storage should ensure traceability (“audit trail”) of all entered or changed data, including the dates and sources of data received and the date and place to which these data are transmitted.
7.1.4.7. The database should be checked regularly to detect and handle duplicate adverse reaction reports during the data entry and generating summary reports.

7.1.5. Quality Management.

7.1.5.1. Authorized authorities of the Member States 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 such stages as data collection, data transmission, data management, data coding and archiving, case validation, case assessment, follow-up information, individual case safety reporting and case archiving). 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 the reaction), or images of the source data.

7.1.5.2. Written standard operating procedures should ensure that roles and responsibilities are clearly defined, and tasks are clear to all parties involved in adverse reaction reporting. Provisions should be developed and implemented to ensure proper control and, if necessary, change the 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.
7.1.5.3. Adequate training should be provided for personnel directly involved in pharmacovigilance activities and personnel from other departments who may be involved in receiving or processing safety reports (e.g., clinical development, sales, health information, legal work, quality control). Training should be provided under the relevant sections of the pharmacovigilance legislation and guidelines and include specific training on how to perform the processing of reports. Personnel charged with data entry should be trained in the appropriate standards and terminology. Personnel in other departments (e.g., clinical development, sales, medical information, legal, quality control) should be trained in collecting and reporting adverse reactions (events) to the pharmacovigilance department following the MA holder's internal policy and local procedures.

7.1.6. Special Situations.

7.1.6.1. Using Medicinal Products While Pregnant or Breastfeeding.

7.1.6.1.1. Pregnancy.

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 substance (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 fetus through the mother or father if the product was taken before conception.

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 can be developed and used to assess such reports.

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 cases include:

- Reports of congenital anomalies or developmental delays in the fetus or child.
- Reports of fetal death and spontaneous abortion.
- Reports of suspected neonatal adverse reactions that are classified as serious.

Other cases such as reports of pregnancy terminations 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.

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 registration 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 products like thalidomide, isotretinoin).

The Member States' authorized 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).

7.1.6.1.2. Breastfeeding.
Suspected adverse reactions in infants after exposure to the medicinal product when it passes into breast milk should be reported.

7.1.6.2. Use of the Medicinal Product in Pediatrics and the Elderly.

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 consumer, to be able to identify potential safety signals specific to a particular age group.

If drug use is common among patient populations not included in the approved general product profile, the Member State's authorized 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 in the Member States 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.

7.1.6.3. Reports of a Drug Overdose, Abuse, and Misuse, as well as Errors of Use or Occupational Exposure to Medicinal Products.

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 procedure. This data should be recorded in an appropriate periodic safety update report and risk management plan (if applicable). If these reports contain safety data affecting the risk-benefit ratio of a medicinal product, they should be notified to the Member States' authorized authorities in accordance with the requirements of these Rules. Following recommendations, the necessary subsequent collection of additional information is performed to ensure complete data regarding symptoms, names of suspected medicinal products,
outcomes, type of non-compliance (e.g., errors of prescription, dispensing, dosing, unapproved indications, etc.).

7.1.6.4. Lack of Therapeutic Efficacy.

Reports of lack of therapeutic efficacy should be recorded and followed up to obtain complete information. These reports are generally not subject to urgent reporting and are included in the evaluation 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-authorization efficacy studies, as components of the primary endpoints of this type of study, are also not eligible for submission.

In the case of detection of therapeutic ineffectiveness cases during antibiotic therapy, it is not required to report issues 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.

For vaccines, cases of lack of efficacy should be reported, in particular, 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-authorization safety studies.

7.1.7. Urgent Submission of Individual Case Safety Reports.

Only valid adverse reaction reports are subject to submission to the authorized authorities of the Member States. The time to complete the urgent reporting procedure begins when the information containing the minimum criteria for submitting a report is made available to a MA holder (including medical representatives and contractors). This date is considered the starting date (“day zero”). It is considered the first day of receipt by the authorized authority or the MA holder of information on a valid individual report about an adverse reaction, including cases of receipt of this information on weekends or holidays.

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 organization (person) and the MA holder to fulfill the obligations to submit valid reports of adverse reactions within the required time frame. These procedures should 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 authorized authorities of the Member States. Duplicate transmission of reports to the authorized authorities of the Member States should be avoided.

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. If the outsourcing person or organization 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 national reporting legislation of a Member State.

If additional critical information is received about a previously submitted 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 follow-up information). When drafting a report, significant 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 severity assessment. Non-material additional information includes updated comments regarding the assessment of the cases performed or the correction of typographical errors in the previous case report.

7.1.7.1. Urgent Submission Requirements for Adverse Reaction Reports.

MA holders, within 15 calendar days from the date of receipt by a MA holder or his authorized representative of the minimum required information in accordance with paragraph 7.1.7 of these Rules, submit to the authorized authority of the Member State:

Report of a serious adverse drug reaction detected in the territory of a Member State.

Report of a suspected unexpected serious adverse drug reaction detected in the territories of other states.

The established reporting period applies to primary and additional information about an adverse drug reaction.

7.1.7.2. Cancellation of an Individual Case Safety Report.

The procedure for cancellation of an individual case safety report must be used to indicate the invalidity of a previously submitted report, e.g. if the
whole case is found to be in error. The procedure for canceling individual case safety reports is determined in paragraph 7.3.9 of these Rules.

7.1.7.3. Modification of an Individual Case Safety Report.

Where it is necessary, e.g., following internal or expert review, to make changes to a previously submitted individual case safety report (e.g., in terms of terminology, severity criteria, assessment of causal link, provision of a translation or article from a medical literature source) that do not meet the requirements for reporting with important additional information, changes may be made as defined in paragraph 7.3.8 of these Rules.

7.1.7.2. Way and the Format for Reporting Adverse Reactions.

MA holders should electronically submit adverse reaction reports to the Member State's authorized authority. The format of adverse reaction reports should comply with the format established by the International Conference's guidelines on Harmonization of Technical Requirements for Medicinal Products for Human Use (hereinafter, ICH) “Clinical Safety Data Management. Data Elements for Reporting Individual Cases of Adverse Reactions” (considering the transition from E2B(R2) to E2B(R3)). When forming an individual report's content, the corresponding terminology of the Medical Dictionary of Regulatory Activities Terminology (hereinafter, MedDRA) must be used. In contrast, the report must use Lowest Level Terms (LLT). MA holders should ensure that the MedDRA supporting service organization recommendations are followed on time to new versions of the MedDRA terminology used.

The procedure for submitting individual reports about an adverse reaction in electronic form is determined by the relevant leadership of the Member States' authorized authorities.

7.2. Collection of Adverse Reaction Reports.

7.2.1. Obligations of the Member States.
Authorized authorities of each Member State should 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 territory.

Authorized authorities of each Member State should take appropriate measures to encourage health professionals in their territory to submit reports of suspected adverse drug reactions to the Member State's authorized authority. Besides, a Member State's authorized authority has the right to impose special obligations on health care professionals to submit reports of suspected adverse drug reactions to the Member State's authorized authority.

To optimize the procedure for submitting information on adverse reactions, standard forms of forms with the possibility of their direct filling by the user should be freely available on the official websites of authorized authorities (authorized organizations) in the information and telecommunications network “Internet” along with information on various ways of presenting information about suspected adverse drug reactions.

The Member States' authorized authorities should ensure that all reports of serious adverse reactions detected in the Member States territories, submitted to the Member State's relevant authorized authority and assessed as valid, should be included in the Member State's unified adverse reactions database.

Authorized authorities of the Member States should apply “gratitude” measures for reporting adverse drug reactions, including providing reporters with additional information on the results of further consideration of reported adverse drug reactions.

When submission of reports of adverse drug reactions by the MA holders, the authorized authorities of the Member States, in the territories of which the suspected adverse reaction took place, have the right to involve
patients and MA holders in these reports' subsequent work. MA holders may be involved in the follow-up on adverse reaction reports received when it is necessary to:

- Obtain important additional information to perform a proper assessment of an adverse reaction.
- Clarify the conflicting data provided in the adverse reaction report.
- Get 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.

Each Member State should ensure that its authorized authority responsible for drug control is informed of any suspected adverse reaction available to any other government agency, department, institution, or organization responsible for patient safety in the country. These reports are submitted to the national database. In cases where reports of suspected adverse reactions were sent directly to other government bodies, departments, organizations, and (or) institutions in this Member State, the authorized authority of the Member State, whose powers include the implementation of pharmacovigilance in the field of drug circulation, should have agreements with them on the exchange of data, for these reports to be sent to this Member State's authorized authority. Information on adverse reactions in these cases must be transmitted to the Member State's authorized authority in the appropriate form of reporting adverse reactions for medical workers and patients in electronic form. This requirement also applies to cases of the development of adverse drug reactions resulting from medical errors.

Data and documents on pharmacovigilance concerning authorized medicinal products are subject to storage in the authorized authority for at least 10 years after the marketing authorization expiration. The legislation of the Member States may specify a longer storage period.
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.

7.2.2. Obligations of the MA Holders

Each MA holder must establish and maintain a system for collecting and recording all reports of suspected adverse drug reactions that come to his or her attention, whether through spontaneous reporting by health care professionals, patients, or consumers or during post-authorization studies. Procedures must be developed and implemented by MA holders to provide accurate and verifiable data for the subsequent scientific evaluation of adverse reaction reports. A MA holder does not have the right to reject and not follow the required procedures for handling reports of adverse reactions if this information is received electronically or otherwise by patients or health care professionals. MA holders must 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 authorized authority.

Pharmacovigilance data and documents for authorized medicinal products are subject to storage by the MA holder for at least 10 years after the marketing authorization expiration. The legislation of the Member States may specify a longer storage period.

The obligation to collect information on suspected adverse reactions by MA holders also applies to reports relating to medicinal products whose possession cannot be excluded based on one of the following criteria specified in the report on suspected adverse reactions to a medicinal product: trade name of the active ingredient, name of the active ingredient, dosage form, batch or route of administration. An exception based on information from the state of origin or the state of development of the suspected adverse
reaction can be used if the MA holder can confirm that the suspected medicinal product has never been placed on this state's market and is not a product that can be brought to this territory as a travel aid (e.g., medicines for malaria treatment).

The MA holder must ensure that all companies that are part of it are informed of all reports of adverse reactions related to the MA holder's medicinal products. This requirement must also be met if a commercial agreement is concluded for one of the MA holder's medicinal products. Information is provided by the organization by the MA holder entering information about incoming adverse reactions into the database and then functioning as a single point of access to safety data.

7.2.2.1. Spontaneous Reports.

MA holders should 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 suitable means. MA holders may use their websites on the information and telecommunications network “Internet” to facilitate the collection of suspected adverse reactions by submitting adverse reaction forms or appropriate contact details for direct communication.

7.2.2.2. Reports Received upon Request.

MA holders should record all reports of suspected adverse reactions occurring in the Member States' territories or beyond and identified during post-authorization studies. These reports upon request include reports from an organized data collection initiated, managed, or funded by MA holders. These communications also include non-interventional postauthorization studies, compassionate use programs, personalized 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-authorization studies, this requirement applies to studies based on primary data collection; the data collection procedure is given in paragraph 7.2.2.2.1 of these Rules.

MA holders must implement and use mechanisms to collect complete and comprehensive information on cases of suspected adverse reactions in the initial reporting of suspected adverse reactions 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' authorized authorities (if applicable) for the investigational (or supplied) medicinal product. MA holders must establish a system that provides the ability to track reports, follow up on adverse reaction reports, and obtain the primary source evaluation results regarding the relationship between the investigational (supplied) 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, must carry out his 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 authorized authority. Adverse reaction data from organized data collection should be reflected in a periodic safety update report.

7.2.2.2.1. Reports Received during Non-Interventional Study.

If suspected adverse reaction data are derived from non-interventional studies, data from studies with primary data collected directly from patients and health care professionals, and studies with designs that rely on secondary use of data (e.g., studies based on the revision of medical health charts or electronic records, systematic revisions or meta-analyses).
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.

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 should be submitted. Investigators should direct other reports to the Member State's authorized 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 (if applicable).

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 summarized in the final study report.

A MA holder has the right to clarify the requirements for the submission of reports of adverse reactions to the Member State's relevant authorized authorities.

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.

7.2.2.2.2. Compassionate Use Program, a Personalized Unauthorized Medicinal Product Use Program.

If a MA holder or health care professional is notified of a suspected adverse reaction or detects a suspected adverse reaction as part of a compassionate use program, out of compassionate reasons or a personalized unauthorized medicinal product use program, adverse reaction reports are submitted as follows:
If an adverse reaction has been detected in the course of organized data collection, only adverse reactions with a causal link to the suspected product should be reported as possible (at a minimum) by the source of the report or by the MA holder. These reports should be considered as adverse reaction reports received upon request.

If an adverse reaction was not detected through an organized data collection, all adverse and unintended reactions to the medicinal product should be considered suspected adverse reaction reports not received upon request and presented as a corresponding report.

7.2.2.2.3. Patient Support Program.

Patient support programs are a type of organized data collection system where a MA holder collects data related to drug use in patient populations. Examples of post-marketing patient support programs are disease monitoring programs, patient monitoring, patient adherence data collection, and monitoring as part of compensation (reimbursement) systems.

It is permissible to actively collect information on adverse reactions during the execution of various types of organized data collection systems. These adverse reactions should be counted as reports received on request. The MA holder must ensure that there is a mechanism for the organized and systematic collection of safety information following the implemented program and ensuring the submission of adverse reaction reports to the authorized authority in accordance with the requirements of paragraphs 7.1.7 and 7.1.6 of these Rules in case of determination of compliance with the criteria for urgent reporting.

If an adverse reaction has been identified in an organized data collection system outside the organized safety data collection process, all adverse and unexpected drug reactions that have been reported to the
MA holder by the health care provider or the patient should be treated as suspected adverse reaction reports upon request and submitted accordingly.

7.2.2.3. Reports Published in the Medical and Scientific Literature.

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 paragraph 7.1.1.1.2 of these Rules and submit detected reports of adverse reactions to the authorized authorities of the Member States in accordance with the requirements of these Rules.

The following reports (information) about adverse reactions identified during the monitoring of publications of scientific and medical literature are not subject to urgent reporting:

If the ownership of a medicinal product by the MA holder can be excluded based on the product's trade name specified in the report, the name of the active substance, dosage form, the route of administration, and the batch number.

If the ownership of the medicinal product by the MA holder can be excluded based on the country of origin of the report or the country of origin of the suspected adverse reaction specified in the report if the MA holder did not supply the product to this territory.

If the publication is the result of analysis by the authorized authority of the Member State of the adverse reactions database, the exception does not apply to publications generated based on the analysis of databases of other authorized authorities.

If the publication contains information from public databases where cases are presented 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.
If the publication presents the results of post-authorization studies, meta-analyses, or scientific reviews.

If 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.

The safety information presented in such scientific publications should be considered in the relevant sections of the periodic safety update report. They should be 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 authorized authority where the product is authorized.

7.2.2.4. Suspected Adverse Reactions Associated with Quality Defect or Adulterated Medicinal Products.

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).

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 related to an adulterated 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' authorized authorities is required.
7.2.2.5. Suspected Transmission of an Infectious Agent Through a Medicinal Product.

An infectious agent is any microorganism, virus, or infectious particle (e.g., transmissible spongiform encephalopathy-associated prion protein), pathogenic or non-pathogenic.

Suspicion of infectious agent transmission through a medicinal product 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 authorized representative of the minimum required information in accordance with paragraph 7.1.7 of these Rules. This requirement also applies to vaccines.

MA holders of medicinal products obtained from human blood or plasma are required to have a system that provides, in case of suspicion of an infectious agent transmission, immediate notification of the product's manufacturer, relevant authorized authorities for controlling the circulation of blood products, and authorized authorities of the Member States.

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 through a medicinal product. Still, the risk of unknown pathogens should also be considered.

Evaluation of suspected transmission of an infectious agent through a medicinal product should be carried out with extreme caution and ensure, as far as possible, a distinction between causes 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).
Confirmation of contamination (including inappropriate inactivation or weakening of virulence (attenuation) of infectious agents as active substances) 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.

7.2.2.6. Emergency Safety Issues.

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, which requires an immediate assessment by the authorized authority and may require urgent regulatory measures, and informing health care professionals and patients. Submission of information on identified emergency safety issues is carried out in accordance with the requirements established in paragraph 9.2.3 of Section 9 of these Rules. If individual cases of suspected adverse reactions were the basis for identifying an emergency safety issue, the requirements for the submission of adverse reaction reports should be met.

7.2.2.7. Submission of Adverse Reaction Reports between Applying for Marketing Authorization of a Medicinal Product and Obtaining Approval.

In the period between applying for marketing authorization of a medicinal product and obtaining approval, the 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 authorized authority that conducts the examination and approval of the medicinal product, in accordance with the requirements of paragraphs 7.2.2.6 and 9.2.3 of these Rules.

Suppose the MA holder receives information about adverse reactions identified during the medicinal product use in other countries. In that case,
valid adverse reaction reports and additional safety information must be submitted to the authorized authority in accordance with paragraph 7.1.7.1 of these Rules.

7.2.2.7. Submission of Adverse Reaction Reports in the Period after Suspension or Withdrawal of a Marketing Authorization of a Medicinal Product.

The MA holder must continue to collect information on suspected adverse reactions associated with the medicinal product in question after the suspension of the marketing authorization with the implementation of reporting in cases that meet the criteria for urgent reporting.

If the marketing authorization is withdrawn, authorized authorities should compel the MA holder to continue to collect 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).

7.2.2.8. Submission of Adverse Reaction Reports during Health Emergencies.

A public health emergency is a public health threat officially identified by the World Health Organization. In the event of a public health emergency, authorized authorities have the right to amend the requirements for the regularity of suspected adverse reactions. Such amendments are adopted separately for each emergency, and notifications about them are posted on the official websites of the Member States' authorized authorities in the information and telecommunications network “Internet.”

7.2.2.9. Submitting Reports Based on Lawsuits for Harm Caused by the Use of Medicinal Products.

Reports arising from lawsuits on drug 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 immediate reporting, valid individual case safety reports shall be submitted to the Member States' authorized authority in accordance with paragraphs 7.1.6 and 7.1.7 of these Rules.

When receiving a large number of potential reports of serious adverse reactions, the MA holder, as an exception, may agree with the authorized authority to extend the deadline for submission of individual reports to 30 calendar days.

7.2.2.10. Reporting Cases of Use of a Medicinal Product Not Following the Summary of Product Characteristics or the Package Insert.

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 drug information (summary of product characteristics or package insert), such as:

The use of a medicinal product not following the approved indications.
Use in a patient group where the product is not recommended to use.
The difference in route of administration.
The difference in the dosage regimen.

The following conditions determine requirements for reporting cases of drug use not following the summary of product characteristics or package inserts according to the result of use regarding harm to a patient's health or life:

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.
In case of receiving information about the development of an adverse reaction, a MA holder takes measures to ensure the subsequent collection of 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 7.1.6 and 7.1.7 of these Rules in case of determination of compliance with the criteria for immediate reporting.

Where applicable, the assessment of the risk-benefit ratio of the medicinal product in the periodic safety update report should include the clinically significant risks of using the medicinal product, not following the approved information for use.

In accordance with Section V 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 of a risk management plan for the medicinal product in the safety specification. This recommendation is especially applicable in cases where the identified aspect of the safety profile is characterized by significant differences between the general population and the population in which the medicinal product was not used following the approved information for use. The inclusion of a safety concern in the list of important potential risks of the risk management plan requires the subsequent implementation by the marketing authorization of measures to assess this important risk as part of the pharmacovigilance plan.
The medicinal product's use is not following the summary of product characteristics or the package insert without causing harm to the patient and a suspected adverse reaction.

The MA holder must 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 authorized authority about all changes in the risk-benefit ratio of the medicinal product. 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, 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 for the 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).
Individual case safety reports for 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 authorized authority since they do not meet the minimum criteria for compliance with valid reports.

Medicinal products that do not have a developed and approved risk management plan should also be assessed by the MA holder and authorized 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-authorization safety study is determined.

7.3. Preparation of Individual Case Safety Reports

7.3.1. General Principles for the Preparation of Individual Case Safety Reports.

Individual adverse reaction information is exchanged electronically using MedDRA terminology and following the applicable E2B electronic data format. The information in the submitted individual report should be as complete as possible to carry out the 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.

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 emergency safety issue that must be submitted to the authorized authority as an individual report and as an emergency safety issue.
in accordance with paragraph 9.2.3 of these Rules. In this case, the reasons for classifying the information in this report as an emergency safety issue and the proposed measures are included in the “Reporter Comments” section according to the electronic data format of the individual E2B adverse reaction report.

7.3.2. Information about Suspected, Interacting, and Concomitant Medicinal Products.

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 authorized authority or the MA holder with the characterization of the role of medicinal products made by the primary source, this discrepancy is reflected in the “Reporter Comments” section according to the electronic data format of the individual E2B adverse reaction report, while retaining the primary assessment of the reporter. 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 country in which the patient received the product, the marketing authorization number, the country in which the product was authorized, and (or) the batch number are also indicated.

7.3.2.1. Suspected Relationship with the Therapeutic Class of a Medicinal Product.
If there is no indication of the trade or international name for the suspected medicinal product (e.g., only the therapeutic class is indicated by the source), or if it is impossible to structure the prescribed therapy, this information is included in the case description section and is not included in the structured elements of these names of products 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 authorized authorities. In this case, the person responsible for submitting the report to the Member States' authorized authorities must take the necessary measures to collect the missing information about the suspected medicinal product.

7.3.2.2. Suspected Drug Interactions.

When describing drug interactions, which may include the interaction between medical products (including biological products), as well as the interaction of drugs with food, medical devices, alcohol, coding the 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-drug interaction, under “Characterization of the Role of the Medicinal Product” for all interacting substances, the characteristic “interacting medicinal product” is selected.

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.
7.3.2.3. Suspicion of an Interaction with a Medicinal Product's Excipient.

If the primary source 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 separately provided under “Information on Medicinal Product,” reflected in the description of the case and, if available, under “Patient Study and Tests Results,” the data of the test results (positive or negative) are given, which suggest the presence of a relationship between an adverse reaction and one of the product's excipients.

7.3.2.4. Important Additional Information on the Medicinal Product.

If there is additional information about the medication that may be important for performing data analysis and case evaluation, it should be included in the report under “Additional Information on the Medicinal Product” with the appropriate section selection and coding of the additional characteristic according to MedDRA terminology attribution: adulterated product, overdose, medication was taken by patient's father, medication was taken after the expiration date, series test results confirmed compliance with specifications, series test results demonstrated deviation from specifications, medical use error, misuse, addiction, exposure due to the occupational activity performed or application not following the summary of product characteristics. The “Reporter Diagnosis” section may include a description of signs and symptoms that support a particular diagnosis or describe the role of the suspect product under “Reporter Comments.” If the reporter does not make specific instructions regarding additional product characterization, but it is evident from the report's clinical context, the reporter may at its discretion add additional product characterization information to the specified section. Still, in this case, follow-up for additional information is
recommended. The free text part of the section “Additional Information on the Medicinal Product” can be used to attach any additional information on this section, for example, data on the expiration date for the specified batch of the medicinal product.

7.3.3. Suspected Adverse Reaction.

The adverse reaction report should include all available information on the suspected adverse reaction reported. The data required include the dates of the onset and the end of the adverse reaction (or duration), the severity of the adverse reaction, the outcome of the adverse reaction at the date of the last observation, the time interval between the initiation of the suspected medicinal product and the onset of the adverse reaction, the description of the adverse reaction by the source, the country in which the adverse reaction has been identified.

The coding of diagnosis, provisional diagnosis, or symptoms and signs is performed using the current version of the MedDRA dictionary and according to the lowest level terms. If the report reports 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 should be reflected using the appropriate MedDRA term. If these symptoms are typical clinical manifestations of a certain diagnosis, this diagnosis can be additionally entered following the MedDRA terminological classification by an authorized authority or a MA holder as part of the diagnosis or the reporter's comment.

When a case report identifies symptoms that are not typical clinical manifestations of the original diagnosis and is suspected of being adverse
reactions, these symptoms should be reported and classified as appropriate according to MedDRA terminology.

Suppose the authorized authority or the MA holder disagrees with the diagnosis reported by the primary source. In that case, the alternative diagnosis may be included in the reporter's diagnosis section, stating the grounds for disagreement with the reporter regarding his or her comments.

In the event of a patient's death, the report should include information on the date and cause of death, including, if available, autopsy data. If it is determined that a patient's death is not related to an adverse reaction and is due to other causes, such as disease development, death should not be used as a measure of the severity of the adverse reaction.

7.3.4. Adverse Reaction Description and Causal Link Assessment.

For each individual report, information on the developed adverse reaction description is provided if the necessary data is available in the primary report. Submission of a description is mandatory for serious adverse reactions. Information about the development of an adverse reaction should 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.

The description should 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. The main results of the autopsy or postmortem examination (if applicable) should be summarized. Information on the case
report is included under “Case Summary” of adverse reaction data in E2B electronic format.

The primary source's comments on the adverse reaction report in terms of diagnosis or causal link assessment are provided under “Reporter Comments” in electronic data format.

Authorized authorities of the Member States 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 source (reporter). Comments, in this case, are presented under “Reporter Comments.”

An assessment of the credibility of the 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 Member State's authorized authority) using different causal link assessment methods. In the electronic data format E2BR3, information on the causal link assessment is reflected under “Medicinal Product—Adverse Reaction (Event).”

7.3.5. Test Results and Instrumental Examination.

The adverse reaction description should include the results of tests and procedures performed to diagnose or confirm the reaction (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 studies should be reported.

Information on the results of analyzes and instrumental studies should be presented in the report in a structured form following the current version of MedDRA terminology under “Results of Tests and Procedures Obtained during Patient Examination” in the electronic E2B format of the data of an
individual report about an adverse reaction, 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. If it is impossible to present information in a structured form, the data can be presented in text form for free text in the section “Results of tests and procedures.”

7.3.6. Additional Documents and Information.

Key information from additional documents to support the adverse reaction data should be included in the appropriate sections of individual case safety reports. In the “Additional Available Documents” section of the electronic format of an individual E2B 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 subsection “Attachments.” 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 must be processed, considering the personal data protection legislation in force in the Member State's territory.

7.3.7. Subsequent Information.

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. To determine the status of an individual case safety report at the recipient level, the date of receipt of the report by the recipient, the unique identification number of the individual report, and the number assigned by the recipient are used. The exact dates of receipt of the report (that is, with the date, month, and year) are mandatory to determine the report's 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 should be kept unchanged at the level of authorized authorities and MA holders, reflected under “International Unique Identifier” and “Date when the Report was First Received” respectively. The identifier assigned by the reporter is included under “Unique Identifier of the Reporter of an Adverse Reaction Report.” Upon receipt of each subsequent information by the MA holder or the authorized authority, the exact date of receipt of the latest information on an adverse reaction report is updated, regardless of the significance of this information in the section “Date of receipt of the latest information on an adverse reaction report” of the electronic format of an individual E2B adverse reaction report. New follow-up information in part of the summary should be included in the report under Case Summary, Clinical Description, Therapeutic Measures, Outcome, and Additional Case Information, with the ability to identify the updated piece of data and, where applicable, in a structured form.

7.3.7.1. Important Follow-Up Information.

The reporter of an adverse reaction report should send follow-up adverse reaction information immediately if new important medical data are received. Important new information means, among other things, new suspected adverse reactions, a change in the causal link assessment, and any new information or data about a change in the original (prior) information about the case, if it affects the medical interpretation of the adverse reaction. The determination of whether new adverse reaction data are considered important new information is based on the medical evaluation of compliance with the above criteria.

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 and (or) the assessment of causal link changes from having any level of relationship to questionable relationship) and report such cases as required for urgent reporting of adverse reactions.

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 under “Other Case Identifiers during Previous Data Transmission.” If the reporter submits additional documents to support a change in a previously completed medical evaluation, the new documents are included under “Additional Documents Available” for individual case safety reports in E2B electronic format.

7.3.7.2. Subsequent Information that Does Not Meet the Criteria for Important Information.

If the subsequent information makes minor changes to the original data and the adverse reaction is assessed, it is not subject to immediate submission. Changes in individual chronological dates during the description and evaluation of an adverse reaction without affecting the assessment either by transferring the case or correcting typos in a previous version of the case or by correcting typographical errors in a previously submitted report are considered minor changes. However, an expert medical opinion should be obtained regarding the relevance of the subsequent 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 the adverse drug effect for a different age group of patients). 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 evaluation of the adverse reaction case.

7.3.8. Changes to the adverse reaction report.

General recommendations for making changes to an individual report about an adverse reaction submitted to an authorized authority are determined by paragraph 7.1.7.3 of these Rules. Amending 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 must 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 paragraph 7.3 for examples of how changes are attributed to an adverse reaction report in paragraph 7.3.7 of these Rules). When making changes to the information in the sections “International Unique Identification Number,” “Date when the Report was First Received from the Source,” “Unique Identifier of the Adverse Reaction Reporter,” “Date of Receipt of the Latest Information on the Adverse Reaction Report,” “Reporter's Organization” 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 under “Basis for Cancellation or Changes.”

Additional documents provided at the request of the authorized 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 under “Attached Documents” in individual case safety reports of E2B electronic format.


The cancellation procedure for an individual case safety report should 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.

Cancellation of previously submitted individual case safety reports is subject to the following principles:

The grounds for cancellation must clearly and unambiguously state why a previously submitted report is not considered valid. For example, stating as grounds for cancellation statements like “the report no longer meets the criteria for reporting” or “the report was submitted in error” is not sufficient justification for the cancellation procedure to be followed.

An individual report can only be canceled by the organization that originally submitted the report.

In case of cancellation of an individual report, it is not subject to subsequent restoration as valid.

Individual follow-up reports to the initially submitted individual report are not subject to cancellation; the complete individual case safety report to which subsequent reports have been generated may be canceled.

Canceled individual reports are subsequently not included in the ongoing scientific assessment of the safety data as they are not considered valid. However, the canceled report should be saved in the reporter and recipient's pharmacovigilance database for subsequent audit.

When performing the cancellation procedure for an individual case safety report in the sections “International Unique Identifier,” “Date when the Report was First Received from the Source,” “Unique Identifier of the
Adverse Reaction Reporter,” “Date of Receipt of the Latest Information on the Adverse Reaction Report,” “Reporter's Organization” remains unchanged, in the “Report Cancellation or Changing” section, the option to cancel the previously submitted individual case safety report is selected, indicating the appropriate basis under “Basis for Cancellation or Changes.” If the subsequent submission of a previously canceled individual report is required, new identification numbers are assigned to the report in the “International Unique Identification Number” sections “Unique Identifier of the Adverse Reaction Reporter.”

7.3.10. Personal Data Protection Legislation.

When performing pharmacovigilance duties in terms of working with adverse reaction data, 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 must be met. If the legislation of a Member State does not allow the personal data transfer to the adverse reactions database of the Union, MA holders or authorized authorities of the Member States during the processing of personal data should ensure the use of coding (depersonalization) with a change in personal data (e.g., last name, first name, address) 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 electronic E2B 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 data.

The MA holders or authorized authorities should organize the application of methods for protecting personal data in such a way that no obstacles are created for the effective and timely exchange and assessment of
safety data; considering the high level of importance of such personal data as age or age group of patients and gender, it is required to save this part of personal data in a visible and non-editable format.

7.3.11. The Use of Language in the Presentation of Individual Case Safety Reports.

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.

In the case of individual case safety reports by MA holders, parts of the original description of the adverse reaction are the source, and the summary description of the adverse reaction shall be submitted

in Russian (or with the inclusion of a translation into Russian) if an adverse reaction is detected on the Member States territory;

in English if an adverse reaction is detected in other countries.

When forming an individual case safety report, under “Reaction (Event)” of the report form in accordance with the source description in the national language, the original text describing the suspected adverse reaction by the source is retained, under “Reaction (Appearance)” of the report form in accordance with the source description with translation, a translation of the original text describing the suspected adverse reaction by the source is presented in Russian in accordance with the requirements of paragraph 7.3.11 of these Rules. Under “Summary, Including a Clinical Description of the Case, Therapeutic Measures, Outcome, and Case Additional Information,” a short description of the suspected adverse reaction is provided in Russian or English in accordance with paragraph 7.3.11 of these Rules.
If the reporter submits additional documents in any of the national languages simultaneously with an individual case safety report, the translation into Russian is submitted by the MA holder in case of a request from the Member State's authorized authority.

7.3.12. Special Situations.

7.3.12.1. Use of Medicinal Products During Pregnancy and Lactation.

When organizing work with reports about the use of medicinal products during pregnancy and lactation, it must comply with the general recommendations defined in paragraph 7.1.6.1 of these Rules.

The following recommendations should be ensured when preparing individual case safety reports resulting from drug use during pregnancy or lactation.

7.3.12.1.1. Development of a Suspected Adverse Reaction in a Child (Fetus), except for Cases of Spontaneous Abortion in Early Pregnancy or Fetal Death.

If a fetus or child exposed to one or more drugs 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 fetal death during pregnancy, information on parent and child (fetus) should be submitted in one individual report. In this case, it is a report for a parent and child (fetus). In the “Patient Characteristics” patient data section, information on the child (fetus) is presented. Data on the mother or father who caused the child (fetus) to be exposed to the suspected medicinal product should be presented in a structured form under “Parent Information for Parent and Child (Fetus) Reporting Cases”. If 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 under “Summary, Including
a Clinical Description of the Case, Therapeutic Measures, Outcome, and Case Additional Information.”

7.3.12.1.2. Development of a Suspected Adverse Reaction in a Parent and Child (Fetus).

With the development of suspected adverse reactions, except for cases of spontaneous abortion in early pregnancy or fetal death during pregnancy, 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 (mother or father) and child (fetus). To establish the relationship between reports for subsequent joint assessment, individual reports should 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.

7.3.12.1.3. No Adverse Reaction in a Child (Fetus).

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 drug intrauterine effects on the child. The section “Characteristics of the patient” includes data on the mother or father of the child (fetus). An individual report cannot be submitted if the parent has not developed an adverse reaction due to using one or more medicinal products.

7.3.12.1.4. Report of Spontaneous Abortion in Early Pregnancy or Miscarriage.

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 under “Patient Characteristics.” If the father takes the suspected
drug, the appropriately structured data element is included in the formed report under “Additional Information on the Medicinal Product” of the individual case safety report in the E2B electronic format.

7.3.12.2. Adverse Reaction Reports Published in the Medical Literature.

When forming an individual case safety report published in medical literature to be submitted electronically, the following sections of the individual case safety report in the E2B electronic format:

The “Literature Source” data section must 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.

A detailed description of the adverse reaction case should be included under “Summary, Including a Clinical Description of the Case, Therapeutic Measures, Outcome, and Case Additional Information.”

At the authorized 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 under “Attached Documents.” 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.

If a publication in the 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.
7.3.12.3. Adverse Reaction Reports due to overdose, development of dependence, use not following the summary of product characteristics, misuse, medication error, or exposure resulting from professional activity.

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 exposure resulting from the professional activity, the appropriate terms of the MedDRA dictionary should be used to correctly reflect the nature of the effect of the medicinal product.

General principles for reflecting the characteristics of using a medicinal product in the E2B electronic data format include the following:

Information on the suspected medicinal product in terms of the trade name and (or) active substance is made based on the information provided by the source of the report about the adverse reaction with inclusion in the sections “Trade name of the medicinal product” and “Name of the active substance.”

Under “Additional Information on the Medicinal Product,” structured data elements are selected that characterize the relevant drug exposure (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. If the source did not make a direct indication of overdose, misuse, misuse, development of dependence, exposure as a result of professional activity, use not following the summary of product characteristics, which can be transformed into the corresponding term of the MedDRA dictionary, but this should from the context of the clinical description of the adverse reaction, the reporter can select the most appropriate, in his opinion, structured data element characterizing the corresponding drug effect, ensuring the subsequent collection of information
and clarification of the assessment from the primary source of the adverse reaction.

Under “Adverse Reaction (Event) Following MedDRA terminology,” appropriate lowest level terms should be used to reflect the nature of the drug exposure and the adverse reaction (a set of adverse reactions) resulting from this exposure. If applicable, according to the results of the evaluation of the report, the reporter fills in the section “Diagnosis ( Syndrome) in the Opinion of a Reporter, Change in the Classification of a Reaction (Event)” of the report form with the inclusion of appropriate justifications under “Reporter Comments.”

In the case of a report about a case of a misuse associated with a medication error (receipt by a patient of a medication other than the prescribed one), under “Characterization of the Role of the Medicinal Product,” select the data item “Medicinal Product Not Prescribed,” in the “Medicinal Product Information” section, data on the prescribed product, indicating the fact that the drug was not prescribed, and information about the wrongly prescribed product.

7.3.12.4. Reports on Lack of Therapeutic Efficacy of Medicinal Products.

When reporting a lack of therapeutic efficacy under “Adverse Reaction (Event) Following MedDRA Terminology,” the lowest level terms of the MedDRA dictionary should be used that best reflects the original description of the suspected lack of therapeutic efficacy. A suspected medicinal product is included under “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, including 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.

7.3.12.5. Adverse Reaction Reports Associated with a Defect in the Quality of a Medicinal Product or the Use of Adulterated Medicinal Products.

7.3.12.5.1. Adverse Reaction Reports Associated with a Defect in the Quality of a Medicinal Product.

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.

General principles for reporting adverse reaction information in the E2B electronic format include the following:

In addition to the obligatory section “Name of the Medicinal Product According to the Primary Source Information,” the section “Information on Medicinal Products” is completed following the information provided by the primary source and according to the recommendations for generating data on suspected, interacting and simultaneously prescribed medicinal products.

Under “Additional Information on the Medicinal Product,” a structured data element is selected if there is a corresponding unambiguous indication in the report of the primary source: the medicinal product after the expiration date, the quality control of the batch, and the medicinal product batch confirmed compliance with the specification requirements, the quality control of the batch and the medicinal product batch confirmed non-compliance with specification requirements.

Under “Adverse Reaction (Event) Following MedDRA Terminology,” appropriate lowest level terms should 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. If
applicable, according to the results of the evaluation of the report, the reporter shall fill in the section “Diagnosis (Syndrome) in the Opinion of a Reporter, Change in the Classification of a Reaction (Event)” of the report form with the inclusion of appropriate justifications in the section “Reporter Comments.”

Additional comments on the medicinal product in text form are included under “Additional Information on the Medicinal Product.”

7.3.12.5.2. Reports of Adverse Reactions Associated with the Use of an Adulterated Medicinal Product.

When reporting adverse reactions associated with the use of a medicinal product, for which the fact of falsification of active substances, excipients, or the product, in general, is suspected or confirmed, in the section “Adverse Reaction (Event) Following MedDRA Terminology,” the MedDRA lowest level terms should be used, which most accurately reflects the information on the adulterated product provided by the source.

General principles for reporting adverse reaction information in the E2B electronic format include the following:

In addition to the obligatory section “Name of the Medicinal Product According to the Primary Source Information,” the section “Information on Medicinal Products” is completed following the information provided by the primary source and according to the recommendations for generating data on suspected, interacting and simultaneously prescribed medicinal products.

Under “Additional Information on the Medicinal Product,” the structured data element “Counterfeit” is selected in case of suspicion or confirmation of the use of an adulterated medicinal product: medicinal product after the expiration date, quality control of the batch and batch of the medicinal product confirmed compliance with the specification requirements,
batch quality control, and the medicinal product batch confirmed non-compliance with the specification requirements.

Under “Adverse Reaction (Event) Following MedDRA Terminology,” appropriate lowest level terms should 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 for which the fact of falsification is suspected or confirmed. If applicable, according to the results of the evaluation of the report, the reporter shall fill in the section “Diagnosis (Syndrome) in the Opinion of a Reporter, Change in the Classification of a Reaction (Event)” of the report form with the inclusion of appropriate justifications in the section “Reporter Comments.”

Additional comments on the medicinal product in text form are included under “Additional Information on the Medicinal Product.”

7.3.12.6. Reports of Suspected Transmission of an Infectious Agent through a Medicinal Product.

When reporting adverse reactions associated with suspected transmission of an infectious agent through a medicinal product, the “Adverse Reaction (Event) Following MedDRA Terminology” section should use the MedDRA dictionary's lowest level terms that best reflect the original information regarding the infectious agent.

7.3.12.7. Suspected Adverse Reaction Reports from Organized Data Collection Systems.

General recommendations for data management of individual case safety reports received during post-approval studies (interventional clinical studies and non-interventional studies) are defined in paragraph 7.2.2.2.1 of these Rules. When individual case safety reports identified during these studies are generated 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.

Recommendations for the management of individual case safety reports received from patient support programs or marketing study programs are defined in paragraph 7.2.2.2.2 of these Rules.

The following guidelines should be considered when generating individual case safety reports from organized data collection programs:

7.3.12.7.1. In the case of the formation of adverse reaction reports for which the protocol of the non-interventional post-authorization study determines the performance of a systematic data collection, or if the application program, for reasons of compassion or individual use, provides for an active collection of safety data, or if reports are received as a result of the implementation of support programs patients or market study, adverse reaction reports are considered received upon request and the data item “Report Received During Study” is selected under “Report Type” if a relationship between the investigational product and an adverse reaction is suspected. Under “Type of study in which an adverse reaction was detected,” the appropriate data item “Other Studies” or “Individual Use by a Patient” is selected. If it is assumed that there is a relationship of an adverse reaction with a 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 drug under study, the data item “Spontaneous Report” is selected under “Report Type.”

7.3.12.7.2. In the case of adverse reaction reports for which the protocol of the non-interventional post-authorization study does not specify the performance of systematic data collection, or in the case of a compassionate use program or a personalized use program that does not provide for the active safety data collection, the adverse reaction reports are
considered by spontaneous reports, and in the “Report Type” section, the “Spontaneous Report” data item is selected if a relationship between the investigational product and the adverse reaction is suspected.

7.3.12.7.3. In the case of an adverse reaction report 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 role of the interaction reaction with the investigational product, reporting of adverse reactions are considered spontaneous reports and under “Reporter Type” the data item “Spontaneous Report” is selected.

7.3.12.8. Obtaining Minimal Missing Information.

When receiving minimal missing information regarding a previously invalid individual case safety report, the following data entry guidelines should be followed:

The date under “Date of the First Receipt of the Report from the Source” should reflect the date of receipt of the initial invalid individual case safety report.

The date under “Date of Last Report Information Received” should reflect the date the minimum missing information was received to ensure that the criteria for the validity of individual case safety reports were met.

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.

A compliance assessment is performed at each date that additional information is obtained.

7.3.13. The Quality of the Electronic Data in an Individual Case Safety Report and the Management of Duplicate Adverse Reaction Reports.
Member States' databases of adverse reactions should 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 must be ensured that the requirements of these Rules for the electronic data format, structuring, and coding of information are met. Authorized authorities of the Member States and MA holders are responsible for the implementation of the following activities:

Implementation of 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.

Ensuring that the consistency of the terminology used is adequately monitored through systematic evaluation or regular evaluation of a random sample.

Compliance with the requirements for the quality, reliability of the information, and the time to submit reports of adverse reactions to the Member States' authorized authorities.

Compliance with the requirements for the quality, integrity, completeness of reports of adverse reactions in accordance with the requirements for structure, format and content.

Performing procedures for managing duplicate adverse reaction reports.

To validate the quality system's conformity, including identifying and managing duplicate reports and fulfilling urgent reporting requirements, MA holders and the Member States' authorized authorities should ensure that regular and risk-based quality system audits are carried out. If a non-compliance of the quality system with the established requirements is identified, corrective actions should be taken, including subsequent audits. The dates and results of audits and subsequent audits shall be documented following the provisions of Section 5 of these Rules.
Following the requirements for maintaining and improving the quality system, MA holders and authorized authorities must ensure a sufficient number of qualified and trained personnel to carry out pharmacovigilance activities. Professionals involved in pharmacovigilance activities should undergo initial and periodic follow-up training following their roles and responsibilities. To document, maintain, and develop personnel competencies, it is required to formulate a training plan and reports, available for evaluation during audits or pharmacovigilance system inspections.

Authorized authorities of the Member States 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 timing of their implementation. The way corrective action is taken and the recommended timeline 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).

MA holders and Member State authorities should work together to manage duplicate reports in such a way as to ensure that potential duplicate adverse reactions are identified, evaluated, acknowledged, and processed.

7.3.14. Electronic Exchange of Adverse Reaction Data between Multiple Reporters and Recipients.

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 organization of adverse reaction data collection processes.
The procedures for the adverse reaction data exchange should be organized and carried out so that during the exchange, the adverse reaction information is not omitted or changed unless new data on the corresponding adverse reaction becomes available to the party participating in the transmission of the individual report.

To improve the quality of the submitted adverse reaction reports, if the reporter reveals errors or inconsistencies in the report, it is recommended to 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 incorrect data structuring.

At all stages of the electronic adverse reaction data exchange, the E2B electronic data format requirements for providing subsequent adverse reaction information must 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.

7.4. Cooperation with the World Healthcare Organization

The Member States' authorized authorities ensure the regular submission of individual reports on detected and suspected adverse drug reactions in their territories to the World Health Organization collaborating center to include information about these cases in the World Health Organization adverse reactions database.
8. Periodic Safety Update Report

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-marketing period.

Authorized authorities of the Member States should 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 authorized authority determines the need for further safety or efficacy studies of a medicinal product, the use of certain actions concerning the approval status of a medicinal product, or changes in the summary of product characteristics to ensure product use when benefits outweigh risks.

8.1. Objectives of the Periodic Safety Update Report

8.1.1. 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-marketing assessment of the risk-benefit ratio of a medicinal product at certain stages of a medicinal product's life cycle.

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.
8.1.2. The MA holder must constantly evaluate and analyze the impact of new data on the risk-benefit ratio, re-evaluate this indicator, and determine the need to optimize the risk-benefit ratio by introducing effective risk management measures and their minimization when new safety information on a medicinal product during its post-marketing use is identified.

8.2. Principles for Assessing the Risk-benefit Ratio in the Periodic Safety Update Report

Assessment of the risk-benefit ratio should be continuous throughout a medicinal product's entire life cycle to protect public health and improve patient safety by implementing effective risk minimization 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. The risk assessment is based on information on all aspects of drug 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 medical literature. The assessment of benefits is based on the results obtained in clinical studies and the results of use in real medical practice for approved indications. An integrated assessment of the risk-benefit ratio should be performed for each of the approved indications and should consider the risks associated with using the medicinal product, not following the summary of product characteristics or the package insert.
The assessment includes the following steps.

8.2.1. Critical analysis of all safety information received during the reporting period, identifying possible identified new signals indicating new potential or identified risks, or supplementing these signals with information on existing knowledge on previously identified risks.

8.2.2. Critical generalization of all safety and efficacy information received during the reporting period for a medicinal product (both in clinical studies 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.

8.2.3. Performing an integral analysis of the risk-benefit ratio based on all cumulative data starting from the date of the first approval of a medicinal product or the date of the first approval to conduct an interventional clinical study in any of the states. If the date of the first approval to conduct an interventional clinical study is not available 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.

8.2.4. Summarizing information on risk minimization measures that may have been carried out during the reporting period and planned risk minimization measures.

8.2.5. Determination of a plan for assessing signals, risks, and (or) proposals for additional pharmacovigilance activities.

8.3. Principles for Preparing a Periodic Safety Update Report

The MA holder must 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 Member State's authorized authority.

8.4. Reference Information

8.4.1. The Following Sources of Reference Information Can Be Used by a MA Holder as Reference Information on a Medicinal Product:

A list of basic data on a MA holder's medicinal product (CCDS), 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 (CCSI). 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 risk and benefit assessments. Suppose the list of product core safety information does not include information on approved indications. In that case, 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 authorized only in one country 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 authorized authority can be used as reference information. If 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 document reporting period should be included in the periodic safety update report as an annex.

The MA holder should 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, Included in the Safety Data Sheet for the Medicinal Product” and, if applicable, in Section 16 “Signals and Risk Assessment” of the Periodic Safety Update Report. These material changes may include the following:

- Changes to sections of contraindications, cautions, and special instructions.
- Additions in the section of adverse reactions and interactions.
- The addition of important new information in the overdose section.
- Exclusion of indications, or other restrictions on the use of the medicinal product, made based on safety data or insufficient therapeutic efficacy.
The MA holder must 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 must have an effective date and are subject to the MA holder's control.

In case of receiving important safety information requiring amendments to the current reference information of the medicinal product, after the date of the end of data collection before the submission of a periodic safety update report to the Member State's authorized authority, this information should be included in Section 14 “Important Information Received after the Completion of the Preparation of the Periodic Safety Update Report,” if possible.

8.5. The Content of a Periodic Safety Update Report

8.5.1. A periodic safety update report should include cumulative data from the date of the first approval of the medicinal product 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.

Since a medicinal product's clinical development may continue at the post-marketing stage, the periodic safety update report should include data from post-marketing or clinical studies 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 should also be included in assessing the relevant risks in a periodic safety update report applicable and justified.
A periodic safety update report should include summarizing information on all sources of significant data on the medicinal product's efficacy and safety, which should be considered when performing the next assessment of the risk-benefit ratio and which are available to the MA holder. Sources of efficacy and safety data that can be used in preparing a periodic safety update include:

- preclinical studies (toxicological and *in vitro studies*)
- spontaneous reporting
- active monitoring methods (e.g., analysis of internal or external databases)
- medicinal product quality studies
- studies to assess the use of a medicinal product
- clinical studies, including studies on disapproved indications
- observational studies, including registries
- patient support programs
- data from systematic reviews and meta-analyses
- MA holder's websites
- published data from medical and scientific literature or abstracts, including information presented at scientific conferences and meetings
- unpublished materials
- data from licensing partners, other sponsors, or study sites
- authorized authorities (all countries of the world)

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 known and identified during the reporting period important safety and efficacy aspects of a medicinal product. The MA holder can
provide the list of sources of information used to prepare the periodic safety update report in an annex to the document.

A periodic safety update report must be developed in the form of a document consisting of sections defined in paragraph 8.5.2 of these Rules; sections' requirements 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.

The level of detail of the information provided in certain sections of the periodic safety update report should 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.

8.5.2. A periodic safety update report should include the following sections:

8.5.2.1. Title Page, Including a Signature of the Person Responsible for Preparing the Periodic Safety Update Report.

8.5.2.2. Summary of the Periodic Safety Update Report.

8.5.2.3. Contents of the Periodic Safety Update Report in Tabular Format.

8.5.2.4. Introduction.

8.5.2.5. Global Approval Status of a Medicinal Product.

8.5.2.6. Measures Taken During the Reporting Period Connected with the Received Safety Data on a Medicinal Product.

8.5.2.7. Changes Made to a Medicinal Product's Safety Data Sheet.
8.5.2.8. Estimation of the Number of Patients Exposed to a Medicinal Product and the Features of Its Use in Medical Practice:
   a. Total number of patients exposed to a product in clinical studies.
   b. Total number of patients exposed to the product according to market data on its use.

8.5.2.9. Summarized Tabular Data
   a. Reference information.
   b. Summarized information on serious adverse events identified in clinical studies.
   c. Summarized information on the data of post-marketing use of a medicinal product.

8.5.2.10. Summary of Significant Data Obtained from Clinical Studies During the Reporting Period
   a. Completed clinical studies.
   b. Ongoing clinical studies.
   c. Long-term follow-up monitoring of patients' conditions.
   d. Other therapeutic use of a medicinal product.
   e. New safety data on the fixed combination medicinal product in use.

8.5.2.11. Data from Non-Interventional Studies.

8.5.2.12. Data from Other Clinical Studies and Data Obtained from Other Sources
   a. Data from other clinical studies.
   b. Medication errors.

8.5.2.13. Data from Preclinical (Non-Clinical) Studies.

8.5.2.14. Medical Literature Data.

8.5.2.15. Other Periodic Safety Update Reports.

8.5.2.16. Insufficient Therapeutic Efficacy of the Medicinal Product.
8.5.2.17. Critical Information Received after the Completion of the Periodic Safety Update Report Preparation.


8.5.2.19. Signals and Risk Assessment
a. Summarized safety information.
b. Signal evaluation.
c. Assessment of risks and new information.
d. Risk characteristics.
e. Risk minimization measures' effectiveness (if applied).

8.5.2.20. Benefit assessment:
a. Important basic efficacy information of the medicinal product.
b. New efficacy information revealed.
c. Characteristics of the benefits.

8.5.2.21. Integrated Risk-Benefit Ratio Analysis For Approved Indications
a. Integrated analysis in the context of the risk-benefit ratio (including the medical need and important alternatives).
b. Evaluation of the procedure for analyzing the risk-benefit ratio.

8.5.2.22. Conclusion of the Periodic Safety Update Report and Suggested Follow-Up Actions.

8.5.2.23. Annexes to a periodic safety update report.

8.5.3. Title page

The title page must contain an indication of the number of the periodic safety update report (reports must be sequentially numbered), the name of a medicinal product and active ingredient, the international birth date, the reporting period (or an indication of the extraordinary procedure for submitting the periodic safety update report at the request of a Member State's authorized authority), the date of the report, the MA holder's data, and
an indication of the confidentiality of the information included in the periodic safety update report. The title page of the periodic safety update report must be approved by a signature.

8.5.4. Summary of a Periodic Safety Update Report.

The content summary aims to summarize the content and the most important information in a periodic safety update report. This section should include the following information:

- Introduction, an indication of the report number and the reporting period.
- Name of the medicinal product, pharmacotherapeutic class, mode of action, indications, dosage form, strength(s), route(s) of administration.
- Assessment of cumulative impact in clinical studies.
- Assessment of the interval of post-authorization application and cumulative impact for this post-authorization period.
- The number of states in whose territories the use of the medicinal product is permitted.
- Summarized information on the assessment of the risk-benefit ratio.
- Taken and proposed actions related to the safety aspects, including significant changes made to the investigator's brochure at the clinical studies stage and the summary of product characteristics at the post-authorization stage or other risk minimization measures.
- Conclusion.

8.5.5. Summary of the Report Should Be Accompanied by a Table of Contents for the Periodic Safety Update Report.

8.6. Requirements for the Content of Each Section of the Periodic Safety Update Report.

8.6.1. The “Introduction” Section of the Periodic Safety Update Report.

The introduction should contain the following information:
International birth date, reporting period, and a serial number of the report.

Name of the medicinal product, pharmacotherapeutic group, mode of action, approved indications, dosage form(s), strength(s), route(s) of administration.

A summary of the populations receiving prescription drug treatment and included in clinical studies.

8.6.2. The “Global Approval Status of a Medicinal Product” Section of the Periodic Safety Update Report.

This section should provide a brief overview, including dates of initial approval, approved indications, authorized dosage forms, and strengths with current approvals as of the report date.

8.6.3. The “Measures Taken During the Reporting Period in Connection with the Safety data of the Medicinal Product” Section of the Periodic Safety Update Report.

This section provides a description of the significant measures taken by the authorized authorities of the Member States, the MA holder, the sponsor of clinical studies, the data monitoring and evaluation committee, the ethics committee based on safety data for the reporting period, both concerning ongoing clinical studies and post-authorization applications that:

Had a significant impact on the risk-benefit ratio of the authorized medicinal product.

Impacted the conduct of a particular clinical trial or the overall clinical development program for a medicinal product.

The section should indicate the grounds for taking these measures and, if necessary, additional information (if any). This part also provides a summary of how to update the status of previously adopted measures.
8.6.3.1. Significant Actions Taken Concerning the Investigational Medicinal Product May Include:

a. Refusal of approval for a clinical study on safety or ethical issues.

b. Partial or complete suspension of a clinical study or a complete early termination of a clinical study due to identified 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 submit a marketing authorization application.

e. Introduction of risk minimization measures, including:

Changes made to the study protocol and safety or efficacy data (e.g., changing the dosage regimen, changing the inclusion or exclusion criteria, introducing additional monitoring measures for study subjects, limiting the study duration).

Study population restrictions or indications:
Informed consent changes related to safety aspects.
Change in the medicinal product composition.

An additional requirement of the Member States' authorized 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.

8.6.3.2. Significant Measures Taken Concerning the Authorized Medicinal Product Include:

a. Refusal of marketing authorization renewal.

b. Suspension or withdrawal of marketing authorization.

c. Measures taken in connection with identifying a quality defect or other quality-related reasons concerning the medicinal product.
d. Introduction of a risk minimization plan, including:

- Significant restrictions in the distribution or the introduction of other risk minimization 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.
- Direct healthcare professional communication.
- The requirement of the Member States' authorized authorities to conduct a post-authorization study.

8.6.4. The “Changes Made to the Reference Safety Information of a Medicinal Product” Section of the Periodic Safety Update Report.

This section lists information on all significant changes made to the reference information on a medicinal product's safety for the reporting period. These significant changes include changes to the sections on contraindications, precautions, special instructions, the addition of information about serious adverse reactions, adverse reactions of particular interest, interaction reactions, important data from ongoing and completed clinical studies, important data from preclinical (non-clinical) studies (e.g., carcinogenicity study). Information on these changes should be presented in the appropriate sections of the periodic safety update report. An annex to the periodic safety update report should contain the version of the reference safety information of a medicinal product with the appropriate changes.

8.6.5. The “Estimation of the Number of Patients Exposed to a Medicinal Product and the Features of Its Use in Medical Practice” Section of the Periodic Safety Update Report.

A periodic safety update report should 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 should be
accompanied by a qualitative and quantitative analysis of the 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 evaluating the use of a medicinal product.

This section should estimate the population's size and characteristics exposed to the medicinal product (including a short description of the method used for the assessment and an indication of the method's limits).

Consistent methods for assessing subject or patient exposure should be used in all sections of a periodic safety update report for a single medicinal product. If it is appropriate to replace the used assessment method, both methods and their calculations should be presented in a periodic safety update report explaining the replacement.

8.6.5.1. The “Total Number of Patients Exposed to a Medicinal Product in Clinical Studies” Subsection of the Periodic Safety Update Report.

This subsection should contain the following information about patients included in clinical studies sponsored by a MA holder (it is recommended to use a tabular format):

a. The cumulative number of study subjects included in ongoing and completed clinical studies 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 (if any) (e.g., grouped by age, gender, race throughout the development program).

c. Important differences between studies concerning the prescribed doses, routes of administration, patient subgroups.
d. If clinical studies were carried out on special groups of patients (e.g., pregnant women, patients with impaired renal, liver, cardiovascular system, and clinically significant genetic polymorphism), data on the exposure should be provided.

  e. If there are significant differences in exposure time between subjects randomized to receive the investigational product or comparator, or inconsistencies in exposure duration between clinical studies, an exposure assessment should be expressed as subject-time (patient-days, months, or years).

  f. Data on the effect of the investigational product in healthy volunteers may be of less value for assessing the product's safety profile in general, depending on the type of adverse reactions observed, especially if patients are exposed to a single dose. Such data should be presented separately with explanations (if necessary).

  g. If serious adverse reactions are indicated in the summarized information on adverse reactions identified in clinical studies, an appropriate indication should be made, if possible, to assess the exposure to a patient.

  h. For certain particularly important clinical studies, the demographic factors of patients should be presented separately.

8.6.5.2. The “Total Number of Patients Exposed to a Medicinal Product Following Its Use on the Market” Subsection of the Periodic Safety Update Report.

Whenever possible, a separate assessment of the cumulative impact (from the international birth date) and the interval (from the date of the end of data collection from the previous periodic safety update report) should be provided. The section should estimate the number of exposed patients and how the determination and assessment were performed. The rationale should be provided if it is not possible to calculate the number of exposed patients. If it is not possible to estimate the number of patients, alternative estimates should be
presented to indicate how they were performed. Alternative indicators of impact assessment are patient-days and the number of prescriptions. Only in cases where these indicators are not available can sales estimates expressed in weight units or doses be used. The concept of the Defined Daily Dose (DDD) can be applied to obtain patient exposure data.

Exposure data should be reported for the following categories of drug use:

8.6.5.2.1. Post-Marketing Use (Excluding Clinical Studies).

An overall rating must be provided. Data should be disaggregated by gender, age, indications, dosage forms, 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).

If a series of reports of adverse reactions suggesting the presence of a signal has been identified, data on the effect of the drug on the relevant subgroup of patients should be provided, if possible.

8.6.5.2.2. Post-Marketing Use in Special Population Groups.

If the drug is used in special populations in the post-marketing phase, available information on the cumulative number of patients exposed and the used calculation method should be provided. Sources of this data may include non-interventional studies designed specifically to generate data for specific population subgroups, including registries. Other sources of information may include collecting data on adverse reactions outside of clinical studies 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 for this section include, but are not limited to, including the following:

a. Pediatric population.

b. Elderly population.
c. Women during pregnancy and lactation.

d. Patients with impaired liver and (or) kidney function.

e. Patients with other important comorbidities.

f. Patients whose disease severity differs from that investigated in the course of clinical studies.

g. Subpopulations with a carrier of genetic polymorphism.

h. Patients with a different race or ethnicity.

8.6.5.2.3. Features of the Use of the Medicinal Product.

If a MA holder becomes aware of certain features of using a medicinal product, a description of these features should be provided. An appropriate assessment and interpretation of safety data should be made. These features, 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). If the information on the characteristics of medicinal product use, which were not accompanied by the development of adverse reactions, is necessary to assess the risk-benefit ratio of a medicinal product, it can be summarized 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 available sources to the MA holder. The section provides data that make it possible to make a quantitative assessment of the characteristics of medicinal product use in medical practice, if any. If relevant data are available, the MA holder can comment on the extent to which the use is supported by clinical protocols, the evidence base for clinical studies, or the lack of generally authorized alternatives. When determining aspects of the use of a medicinal product not corresponding to the reference information, the MA holder should use the version of the relevant section of reference information that is valid as of the end of the reporting period of the periodic
safety update report (e.g., approved indications, route of administration, contraindications).

8.6.6. Summarized Tabular Data Section of the Periodic Safety Update Report.

The purpose of this section is to provide data on serious adverse reactions and events identified during clinical studies, spontaneous reports of serious and non-serious adverse reactions received at the post-marketing stage (including reports from healthcare professionals, consumers, publications in medical and scientific literature, data from authorized persons all over the countries) and serious adverse reactions from non-interventional study and other organized data collection programs in the form of summarized tabular data. The MA holder may display certain aspects of the data in graphical form to facilitate perception and understanding.

Data on adverse reactions in a summarized tabular form are presented using MedDRA terminology at the level of preferred terms and system organ classes.

The classification of adverse reactions as serious adverse reactions in the summarized tabular data must comply with the criteria of severity established by the terminology of these Rules. If an individual report of an adverse reaction includes serious and non-serious adverse reactions, in the summarized tabular data, an indication of the severity is made individually for each reaction. The severity score should not be changed when preparing data for inclusion in the periodic safety update report.

8.6.6.1. The “Reference Information” Subsection of the Periodic Safety Update Report.

This subsection specifies the version of the dictionary used to represent adverse events and reactions.
8.6.6.2. The “Summarized Information on Serious Adverse Events Identified During Clinical Studies” Subsection of the Periodic Safety Update Report.

This subsection should provide the rationale for the annex, which includes cumulative summarized tabular data on serious adverse events that have been identified in clinical studies organized by a MA holder, starting from the development international birth date until the date of the end of data collection for the current periodic safety update report. The MA holder must 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 should 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.

The following aspects should be considered:

Providing information on causation is important when evaluating 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 useful to present data showing the relationship between dose and frequency of adverse reactions.

The summary tabular data for serious adverse events identified during 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 criteria for serious events is included in the clinical study report.
The summary tabular data should include both blinded and unblinded data on serious adverse events in clinical studies. Blinded data can be reported from completed clinical studies 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 blinding directly in connection with preparing a periodic safety update report.

Certain adverse reactions can be excluded from the summary information, but all such exclusions should 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.

8.6.6.3. The “Summarized Information on the Data of Post-Marketing Use of the Medicinal Product” Subsection of the Periodic Safety Update Report.

This section provides the rationale for an annex, which includes in a tabular form summarizing data on adverse reactions cumulatively for the entire period and the reporting period, from the international birth date of a medicinal product to the date of the end of data collection, includes information on adverse reactions obtained in the course of non-interventional studies and spontaneous reporting, including data from medical and pharmaceutical professionals, consumers, patients, the Member States' authorized 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, should be reported in one table. The data should be distributed according to the MedDRA classification by organ function classes in the table. For critical safety aspects, separate tables of adverse reactions can be presented with data grouping according to indications, route of administration, and other parameters.
8.6.7. The “Summary of Significant Data Obtained from Clinical Studies During the Reporting period” Section of the Periodic Safety Update Report.

This section should provide a summary assessment of the clinically important efficacy and safety data identified during the reporting period when a MA holder conducted clinical studies. Where possible, data should be categorized by gender and age (especially adult and pediatric populations), indication, dosage regimens, and regions.

Signals identified during clinical studies should 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 of the Periodic Safety Update Report “Signal Evaluation.” New information on previously known potential or identified risks, which is not assessed as a newly identified signal, is reflected in Section 16.3, “Risk Assessment and New Information” and 16.4 “Risk Characteristics” of the Periodic Safety Update Report.

Safety and efficacy data from clinical studies where the marketing authorization was not a sponsor is reported in other relevant sections of the periodic safety update report.

This section provides summarized information from clinical studies 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 the Periodic Safety Update “Insufficient Therapeutic Efficacy in Controlled Clinical Studies.”

In an annex to this section, a MA holder must submit a list of interventional clinical studies organized by him, 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 for each from the study:

Clinical study identifier (e.g., study protocol number or another identifier).

Study title (abbreviated name, if applicable).

Study type (e.g., randomized clinical study, cohort study, a case-control study).

The population under study, including country and other characteristics of the population (e.g., pediatric population or patients with renal impairment).

Study status: in progress (study started and ongoing) or completed (clinical study report completed).

8.6.7.1. “Completed Clinical Study” Subsection of the Periodic Safety Update Report.

This subsection should summarize the clinically important efficacy and safety data from clinical studies completed during the reporting period. This information should be presented in a condensed form or the form of a synopsis. It can include information that confirms or refutes previously identified safety signals and evidence for new safety signals.

8.6.7.2. The “Ongoing Clinical Studies” Subsection.

If a MA holder becomes aware of any clinically important information obtained in ongoing clinical studies (e.g., identified during an interim safety analysis or as a result of the blinding of identified serious adverse events), this section should summarize the new safety information. This subsection may also include information that confirms or disproves previously identified safety signals and evidence of new safety signals.

8.6.7.3. The “Long-Term Follow-Up Monitoring of Patients” Subsection of the Periodic Safety Update Report.
Long-term follow-up data are available for patients included in clinical studies. This subsection provides information on long-term follow-up data relevant to the safety profile.

8.6.7.4. The “Other Therapeutic Use of the Medicinal Product” Subsection of the Periodic Safety Update Report.

This subsection should include clinically relevant safety information from other marketing authorization programs using specific protocols that systematically collect safety data (e.g., accessibility programs, compassionate use programs, individual access, etc.).

8.6.7.5. The “New Safety Data for the Use of the Fixed Combination Medicinal Product” Subsection of the Periodic Safety Update Report.

Unless otherwise specified by the authorized authorities of the Member States, the following data should be provided for combination therapy:

a. If a medicinal product is approved for use as a component of fixed therapy or a multicomponent therapy regimen, the subsection should summarize important safety data of the combination treatment.

b. If the medicinal product is a combination product, this subsection should summarize important safety information for each of the individual components.

8.6.8. The “Non-Interventional Study Data” Section of the Periodic Safety Update Report.

This section summarizes safety information or data derived from non-interventional clinical studies (e.g., observational studies, epidemiological studies, registries, active monitoring programs) organized 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.
The MA holder must include in an annex to the periodic safety update report a list of all non-interventional studies organized 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 minimization measures that were performed or are being carried out during the reporting period (e.g., post-authorization safety studies) with an indication of information on each of the studies in accordance with paragraph 8.6.7 of these Rules.

Final reports prepared during the reporting period should be included in an annex to the periodic safety update report.

This section may include summarized 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.

8.6.9. The “Data from Other Clinical Studies and Data from Other Sources” Section of the Periodic Safety Update Report.

8.6.9.1. The “Data from Other Clinical Studies” Subsection of the Periodic Safety Update Report.

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 studies to which a MA holder had access in the reporting period (for example, the results of meta-analyses of randomized clinical studies, safety data from the development partners of a medicinal product, etc.).

8.6.9.2. The “Medication Errors” Subsection of the Periodic Safety Update Report.
The subsection should 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 application 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.

8.6.10. The “Data from Preclinical (Non-Clinical) Studies” Section of the Periodic Safety Update Report.

This section summarizes information relevant to the safety profile from \textit{in vivo} and \textit{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 should be presented in the section regardless of the data obtained. An assessment of the impact of the obtained data on the safety profile should be presented in the “Signals and Risk Assessment” section of the Periodic Safety Update Report and the “Integrated Analysis of the Risk-benefit Ratio by Approved Indications” section of the Periodic Safety Update Report.

8.6.11. The “Medical Literature Data” Section of the Periodic Safety Update Report.

The section presents a summary of new and relevant safety data published in the peer-reviewed scientific literature or were obtained from unpublished monographs relevant to a medicinal product and became available to a MA holder during the reporting period.
A literature search for preparing a periodic safety update report should be broader than a literature search for individual case safety reports. It should also include studies that have assessed safety outcomes in study groups.

Special safety aspects that should 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.
- Use of a medicinal product in programs of compassionate use and personalized prescription.
- Lack of efficacy of a medicinal product.
- Asymptomatic overdose, inappropriate general characterization of the medicinal product, and inappropriate use of the medication.
- Application errors that were not accompanied by the development of adverse events.
- Important results of preclinical studies.

If applicable, this section should also analyze information on other active substances of the pharmacological group to which the medicinal product belongs.

8.6.12. The “Other Periodic Safety Update Reports” Section of the Periodic Safety Update Report.

This section is created only in cases where, by agreement with the Member States' authorized authorities, a MA holder prepares more than one periodic safety update report for a 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 must prepare one periodic safety update report for one active substance (unless
otherwise determined by the authorized authority). In special cases, by decision of the Member States' authorized 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 should be summarized, unless such a summary is presented in other sections of this report.

If there is access, based on contractual agreements, to the data of the periodic safety update report of other MA holders, sponsors of clinical studies, or other partners for similar medicinal products, the MA holder must summarize the significant safety data obtained from the periodic safety update reports for the reporting period.

8.6.13. The “Insufficient Therapeutic Efficacy of a Medicinal Product Established in Controlled Clinical Studies” Section of the Periodic Safety Update Report.

If, when performing clinical studies for drugs that are used for the treatment and prevention of serious and life-threatening diseases, data are obtained that may indicate their insufficient therapeutic efficacy or insufficient therapeutic efficacy concerning the treatment being carried out, then such data indicate the presence of a significant risk for the target population and should be analyzed and summarized in this section of the periodic safety update report.

8.6.14. The “Important Information Received after the Completion of the Preparation of the Periodic Safety Update Report” Section of the Periodic Safety Update Report.

This section summarizes potentially important safety and efficacy data obtained after the end of data collection but before the finalization of the periodic safety update report. Examples of important data include significant clinical data from new publications, significant patient follow-up data, clinically important toxicological data, and all actions taken by the MA holder,
independent data review committees, and the Member State's authorized authorities regarding product safety concerns. New individual case safety reports should not be included in the section unless they may represent a critical event that confirms the presence of an adverse reaction (e.g., the first reported case of an important adverse event in a person), or 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 for a medicinal product (e.g., a new adverse reaction, caution, or contraindication).

This section should be considered when compiling the “Risk and New Information” subsection of the “Signals and Risk Assessment” section of the periodic safety update report.

8.6.15. The “Signal Review (New, Pending, and Completed)” Section of the Periodic Safety Update Report.

The purpose of this section is to provide as complete a review as possible of the identified signals, signals that were received during the adverse reaction assessment period, and signals for the reporting period, the assessment of which has already been completed. This section should include the signals for which the first stage of the evaluation has been completed, and according to the validation results, the validity of the subsequent stages of the evaluation is determined. Signals can be identified by a qualitative method (e.g., based on the receipt of one or a series of reports of an adverse reaction) 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 authorized authority (any country in the world).

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 available data, in Section 16 of the Periodic Safety Update Report “Signal or Risk Assessment.”

Newly identified signals include signals that were identified during the reporting period. New clinically relevant information obtained during the reporting period regarding a previously closed signal should 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 alarms may be classified as closed or pending, depending on these alarms' status at the end of the periodic safety report reporting period. Examples of attributing signals to new signals in a periodic safety update report include receiving new information from which the following actions have been evaluated:

- Resumption of 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 severity or frequency of occurrence for a particular subgroup of patients were determined.

- It is assumed that precautions or special indications, restrictions on indications or target populations, or other risk minimization measures will need to be added if the potential risk is confirmed.
In this section, or an annex to the section, the MA holder must provide in tabular form the following information on the signals considered or closed as of the end of the reporting period:

- A short description of the signal.
- Date of detection of the signal by the MA holder.
- Signal status as of the end of the reporting period (pending or completed).
- Signal closing date, if applicable.
- A short summary of key data.
- Plans for further signal evaluation.
- Actions taken or planned.

A detailed description of closed signals' evaluation is not included in this section and should be presented in subsection 16.2, “Signal evaluation” 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.”

If a MA holder, at the request of an authorized authority, assessed a certain problem associated with the use of a medicinal product and is not assessed as a signal, and the results of the analysis did not confirm the attribution of this problem to a signal, the section provides summarized information describing the estimation results obtained. If based on the assessment results performed, the problem is attributed to signals; the information should be included in the table data on signals in subsection 16.2, “Signal Assessment” of the Periodic Safety Update Report.

8.6.16. The “Signals and Risk Assessment” Section of the Periodic Safety Update Report.

The purpose of this section is to present:
A summary of known and unknown aspects of the characterization of important identified, significant potential risks, and important missing information is the beginning of the periodic safety update report's reporting period.

Evaluation of all signals closed for the reporting period.
Assessing new information on significant previously identified and significant potential risks.
Summary of the effectiveness of risk minimization measures.

This section's information should not duplicate the data presented in other sections of the periodic safety update report and should 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 summarized analytical information. Still, the description of the clinical assessment of individual cases can be justified if these cases provide characterization and clinical assessment of the risk manifestation.

8.6.16.1. Summarized Safety Information, the subsection of the Periodic Safety Update Report.

8.6.16.1.1. The purpose of the subsection of the periodic safety update report is to summarize information on important safety aspects that are safety concerns for the medicinal product, indicating, for each safety aspect, information on what new information and new assessment on these aspects can be made.

In 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' individual condition.

b. Frequency, predictability, preventability, and reversibility of risk.
c. Potential impact on public health (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 (e.g., refusal of the vaccination program).

8.6.16.1.2. The summarizing information should represent the available safety information for a medicinal product as of the beginning of the reporting period of the periodic safety update report and reflect:

Significant identified risks.
Significant potential risks.
Significant missing information.

8.6.16.1.3. For medicinal products with a safety specification, the information included in this subsection should be consistent with the summarized information provided in the current version of the safety specification at the start of the reporting period of the periodic safety update report.

Concerning medicinal products that do not have a safety data sheet, this subsection should provide information about the important identified potential risks and important missing information related to the product's use based on the pre-marketing and post-marketing period. Examples may include the following information:

Significant adverse reactions.
Information about interactions with other medicinal products.
Identified application errors.
Interaction with food or other substances.
The results of exposure when performing professional activities.
Class pharmacological effects.
Synthesis of important missing information should assess the severity of gaps in available knowledge on certain target populations' safety aspects.

8.6.16.2. The “Signal Assessment” Subsection of the Periodic Safety Update Report.

8.6.16.2.1. The information provided in this subsection should summarize the results of the safety signal assessment that was completed during the reporting period. Signals can be closed based on an evaluation conducted due to signal rejection or signal confirmation and attributed to the number of significant potential or identified risks. The subsection includes an assessment for two categories of signals:

a) Based on the assessment results, signals that can be classified as potential or identifiable risks, including the lack of therapeutic efficacy.

b) 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 must 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 should reflect 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. It is recommended that the information be presented in the following order when more than one signal in two categories is included in the evaluation data section:

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.

Closed signals, defined as identified risks and not classified as important.

The evaluation of closed signals should be presented in terms of readings or populations where applicable.

8.6.16.2.2. A description of the signal assessment performed should be included in this subsection of the periodic safety update report or presented as an annex. The description of the assessment should include the following aspects:

a. Source or driving moment of the signal formation.

b. Rationale relevant to the assessment.

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 standardized MedDRA queries) or analytical approaches.

d. Critical analysis results (summarized information) of the data considered when evaluating the signal; in cases where this is important, the results may include a description of a series of cases or an individual representative case of an adverse reaction).

e. Discussion.

f. Conclusion, including proposed actions.

8.6.16.3. The “Risk and New Information Assessment” Subsection of the Periodic Safety Update Report.

A MA holder must submit a critical assessment of new information for the reporting period concerning previously identified risks, which is not 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 should be presented in a tabular signal data format and included in the assessment in Section 16.2 “Signal Assessment” if the signal is 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 characterization of a previously identified risk.

New information should be submitted under the following sections:

New information on significant potential risks.
New information on significant identified risks.
New information on other potential risks not categorized as significant.
New information on other identified risks not categorized as significant.

Update on significant missing information.

The main emphasis of the presented assessment should be made on new information received during the reporting period and a reasonable interpretation of the impact of the obtained data on the understanding and characterizing risks. Based on the impact assessment performed, an update of the characteristics of important potential and significant 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.

A description of the assessment of new information carried out, or an update of missing information should be included in this subsection of the
periodic safety update report or presented as an annex. The description of the assessment should include the following aspects:

a. Source or driving moment of the signal formation.

b. Rationale relevant to the assessment.

c. Assessment methods, including data sources, search criteria, or analytical approaches.

d. Critical analysis results (summarized information) of the data considered when evaluating the signal.

e. Discussion.

f. 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 should reflect and critically evaluate all new information regarding the populations exposed to the medicinal product during the reporting period and obtain data on aspects of the missing information. Unresolved concerns and aspects of data uncertainty are to be objectively pointed out.

8.6.16.4. The “Risk Characteristics” Subsection of the Periodic Safety Update Report.

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 important missing information.

8.6.16.4.1. Considering the source of the data, the risk information should include the following (if applicable):

a. Frequency.

b. Number of cases detected (numerator) and the estimate's accuracy, considering the data source.
c. Volume of prescriptions (denominator), expressed as the number of patients, patient–months (years), etc., and the estimate's accuracy.

d. Assessment of the relative risk and its accuracy.

e. Assessment of the absolute risk and its accuracy.

f. Impact on the patient (symptoms, quality, and number of years of life).

g. Impact on public health.

h. 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).

i. Dose, route of administration.

j. Duration of treatment, period of risk.

k. Preventability (predictability is assessed, the ability to monitor the condition by indicator symptoms or laboratory parameters).

l) Reversibility.

m) Potential mode of action.

o) Level of evidence and uncertainty, including analysis of conflicting facts (if any).

If the missing information is assessed as an important risk, this aspect of the missing data is included in the list of safety concerns. Information to be provided reflecting the limitations of the available database (considering the number of patients included in the study, cumulative exposure or long-term use, and other restrictions).

8.6.16.4.2. 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 following sections may be presented:
a. Risks specific to the active substance.

b. Risks specific to certain dosage forms or routes of administration (including exposure during professional activities).

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).

8.6.16.5. The “Effectiveness of risk minimization measures (if applicable)” Subsection of the Periodic Safety Update Report.

Risk minimization measures include actions to prevent adverse reactions associated with exposure to the medicinal product or to reduce the severity of their occurrence. Risk minimization activities aim to reduce the likelihood or severity of adverse drug reactions. Risk minimization measures include routine risk minimization measures (e.g., changes in the summary of product characteristics) or additional risk minimization measures (e.g., direct information sharing with healthcare professionals or educational materials).

The subsection should present the results of evaluating the effectiveness of risk minimization measures. The relevant information on the effectiveness and (or) restrictions of specific risk minimization measures for important identified risks, which was received during the reporting period, is presented in a summarized form. The assessment results of the effectiveness of risk minimization measures carried out in one of the territories or in a region, which can be useful and used when implemented in other countries' territory, are important and must be presented. The results of assessing the effectiveness of risk minimization measures obtained during the reporting period in a particular region are presented in the regional annex to the report.

8.6.17. The “Assessing Benefit” Section of the Periodic Safety Update Report.
In this section, subsections 17.1 “Important Core Efficacy Information on the Medicinal Product” and 17.2 “Newly Identified Efficacy Information,” presents the main obtained and newly revealed efficacy information, which forms the character of the benefit of the medicinal product, the description of which is to be presented in subsection 17.3 “Benefit Characteristics” with subsequent inclusion in Section 18 “Integrated Assessment of the risk-benefit Ratio of a Medicinal Product” of the Periodic Safety Update Report.

8.6.17.1. The “Important baseline information on the effectiveness of the medicinal product” Subsection of the Periodic Safety Update Report.

This subsection summarizes the basic information on the medicinal product's efficacy in clinical studies and its efficacy when used in medical practice from the beginning of the reporting period. This information must be relevant to the approved indications for use in the medicinal product's reference information.

For medicinal products with multiple indications, target populations, and (or) routes of administration, the benefits should be characterized separately for each factor.

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 the “Benefit Characteristics” subsection of the periodic safety update report. The content and level of detail of the information provided in the section should be sufficient to justify the benefit characteristics in subsection 17.3 “Benefit Characteristics” and the assessment of the risk-benefit ratio in subsection 18 and may include (if necessary) the following aspects:

Epidemiology and origin of disease.
Benefit characteristics (e.g., diagnostic, preventive, symptomatic, disease-modifying).

Important endpoints supporting benefit (e.g., effects on mortality, symptomatology, outcomes).

Evidence of efficacy in clinical studies and medical practice compared with a comparator (e.g., comparative controlled clinical studies, meta-analyses, observational studies).

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.

8.6.17.2. The “New Revealed Efficacy Information” Subsection of the Periodic Safety Update Report.

For medicinal products during the reporting period, new information on efficacy in clinical studies and medical practice may be obtained, which should be presented in a subsection. This subsection may provide new information on efficacy in real medical practice if available for approved indications. Separate information on the evidence base for disapproved indications is not included in the section unless it is relevant to the assessment of the risk-benefit ratio.

When used for new indications that were approved during the reporting period, efficacy information on the medicinal product is also subject to reflection in this subsection. The content and level of detail of the information provided in the section should 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.”
This subsection focuses on vaccines, anti-infectious agents, and other products for which changes in the therapeutic environment may affect the risk-benefit ratio over time.

8.6.17.3. The “Benefit Characteristics” Subsection of the Periodic Safety Update Report.

This subsection provides a consolidated baseline and emerging therapeutic benefit data that became known during the reporting period for approved indications.

If there are no new data on the benefit characteristics and no significant changes in the safety profile, this subsection should contain a reference to the subsection “Important Core Efficacy Information on the Medicinal Product Obtained During Clinical Studies and Use in Medical Practice” of the periodic safety update report.

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.

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, the section should provide a brief critical assessment of the evidence base for safety and efficacy in clinical studies and medical practice, indicating the following information:

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 different studies data).

New information that questioned surrogate endpoints (if any).

Clinical significance of the severity of the therapeutic response.
Generalizability of the therapeutic effect between target subgroups (e.g., information about the lack of therapeutic response for any population subgroup).

Adequacy of dose–response relationship.
Duration of the effect.
Comparative efficacy.

Determination of the extent to which efficacy data obtained from clinical studies can be summarized to the population in which a product is used in medical practice.

8.6.18. The “Integrated Analysis of the Risk-benefit Ratio for Approved Indications” Section of the Periodic Safety Update Report.

In the section, the MA holder must present a summarized assessment of the medicinal product's benefits and risks when used in clinical practice. Provides a critical analysis and consolidated information on the previous sections in terms of benefits and risks without duplication with information in the subsections “Risk and New Information Assessment” and “Benefit Characteristics” of the periodic safety update report.


This subsection summarizes the medical need for a medicinal product for approved indications by alternatives (conservative treatment, surgery, or other indications, including no treatment).

8.6.18.2. The “Assessment of the Procedure for Analyzing the Risk-benefit Ratio” Subsection of the Periodic Safety Update Report.

The risk-benefit ratio has different values depending on the indication and target populations. Therefore, for medicinal products authorized for several indications, the risk-benefit ratio should 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 should be presented separately and for population subgroups (if possible).

8.6.18.2.1. Core information regarding the assessment of benefits and risks, which should be presented in the subsection:

Key information provided in the preceding sections on benefits and risks should be combined to assess their ratio.

The context of the drug use (cure, prevention, diagnosis), the severity and seriousness of the disease, the target population (relatively healthy, chronic diseases) are assessed.

Concerning benefits, its nature, clinical significance, duration 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, the severity of the effect, individual elements of benefit are assessed.

Concerning risk, the clinical significance is assessed (e.g., the nature of toxicity, severity, frequency, predictability, preventability, reversibility, effect on the patient), and the risk aspects associated with unapproved indications, new indications, misuse.

When formulating an assessment of the risk-benefit ratio, weaknesses and strengths and uncertainties in the evidence base for benefits and risks are considered, with a description of their impact on the assessment. A description of the restrictions of the assessment is given.

8.6.18.2.2. A description and argumentation of the methodology used for assessing the risk-benefit ratio is presented:

a) Assumptions, considerations, correlations, which confirm the conclusion made on the assessment of the risk-benefit ratio.
6) Comments on the possibility of expressing benefits and risks as presented and comparing them.

b) A summary description of the assessment methods is included if a formal quantitative or semi-quantitative assessment of the ratio is presented.

g) Economic assessment (e.g., cost–effectiveness) should not be considered when assessing the risk-benefit ratio.

In case of receiving new significant information or preparing a periodic safety update report at the authorized 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. If insignificant new information was received during the reporting period, the main focus of the assessment of the risk-benefit ratio should be to update the safety assessment of a medicinal product.

8.6.19. The “Conclusion of the Periodic Safety Update Report and Suggested Follow-Up Actions” Section of the Periodic Safety Update Report.

The final section of the periodic safety update report should 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).

Based on the assessment of cumulative safety data and the risk-benefit ratio analysis, a MA holder should assess the need to change the reference information for a medicinal product and propose the context for the changes.

If necessary, the conclusion should include preliminary proposals for optimization or further assessment of the risk-benefit ratio with a view to their subsequent discussion with the Member States' authorized authorities. These proposals may include risk minimization measures.
For medicines included in pharmacovigilance and risk minimization plans, proposals should be added to the pharmacovigilance and risk management plans.

Based on the assessment of cumulative safety data and an assessment of the risk-benefit ratio, the MA holder must conclude the periodic safety update report regarding the need to amend the reference information for the medicinal product and (or) perform additional pharmacovigilance activities or risk minimization measures. Proposed changes to the medicinal product's reference information (summary of product characteristics and package inserts) should be described in this section.

8.6.20. The “Annexes to the Periodic Safety Update Report” Section of the Periodic Safety Update Report.

The section should include the following annexes:

a. Reference information.

b. Cumulative summary tabular data for serious adverse events identified in clinical studies; cumulative and interval summarizing tabular data on serious and non-serious adverse reactions according to post-marketing 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-marketing interventional and non-interventional safety studies sponsored by the MA holder aims to identify, characterize and quantify safety concerns, or confirm the safety profile of the medicinal product evaluate the effectiveness of risk minimization 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. Proposed additional pharmacovigilance activities and risk minimization measures. The annex should include an indication of the MA holder's planned submission of the risk management plan or the update of the risk management plan.

h. Summarized information on the medicinal product's safety concerns following the revision of Module CVII of Section II of the Risk Management Plan as of the beginning of the reporting period.

i. Final reports of post-marketing 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 evaluate the effectiveness of risk minimization measures.

j. Reports on the results of studies or other activities to assess the effectiveness of risk minimization measures.

8.7. Quality System for the Periodic Safety Update Report at the MA Holder Level

A MA holder should have established structures and processes for the preparation, quality control, review, and submission of a periodic safety update report, including control of performance during and after their assessment. These structures and processes should be described in procedures adopted in the form of a written document, the MA holder's quality system.

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 studies, literature review, detection, validation, and assessment of the signal, additional measures on pharmacovigilance and post-authorization study activities, procedures for processing and combining data
in assessing benefits and risks, etc.). The quality system should describe the relationship between processes, information channels, and responsibilities for procedures to collect all relevant information for inclusion in the periodic safety update report. Documented procedures for controlling the quality of the processes should be developed and implemented to ensure the data's completeness and accuracy in the periodic safety update report. The importance of an integrated risk-benefit assessment determines the need to provide input from various departments or divisions when preparing a periodic safety update report.

The periodic safety update report should contain an assessment of special requests for safety profile aspects by the Member States' authorized authorities. The MA holder must develop and implement a mechanism to ensure proper processing and responses to requests from the Member States' authorized authorities.

The submission of summarized tabular data should be subject to a data verification procedure concerning the MA holder's databases to ensure the accuracy and completeness of the submitted data regarding adverse reactions and events. The processes for placing queries in the database, the parameters used to retrieve the data, and quality control should be properly documented.

The MA holder's proper quality system must eliminate the risk of the registrant's failure to comply with legal requirements, such as:

Failure to submit a report: 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' authorized 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' authorized authorities.

All significant deviations from the procedure for preparing and submitting a periodic safety update report should be documented, and appropriate corrective and preventive actions taken. This documentation should be available at all times.

In the case of delegation of responsibilities for preparing a periodic safety update report to third parties, the MA holder must ensure that the third party has an adequate quality system that meets the requirements of the right of the Union and the legislation of the Member States.

8.8. Training of Personnel on Procedures for Periodic Safety Update Report

The pharmacovigilance officer's responsibility is to ensure that pharmacovigilance, health information assessment, and quality control personnel are involved in the preparation, review, quality control, evaluation, and submission of a periodic safety update report are properly experienced, qualified, and trained. The necessary training should be provided in the various processes, aspects of knowledge, and skills associated with pharmacovigilance. Areas of training should include aspects of Union law and the legislation of the Member States, guidelines, scientific assessment of data, written procedures on preparing a periodic safety update report. Documentation of the training process should confirm its completion before the respective functions' initiation for a periodic safety update report.
8.8. Procedure for Submitting a Periodic Safety Update Report


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' authorized authorities.

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 date of the end of data collection.

8.8.2. The Procedure for Submitting a Periodic Safety Update Report for Generics, Well-Established Use Products, Herbal Medicinal Products, Homeopathic Products Authorized or Aligned with the Right of the Union.

A periodic safety update report for generics, well-established use products, herbal medicinal products, homeopathic products authorized or aligned with the right of the Union shall not be submitted, except in the following cases:

- Obligation to submit a periodically updated safety report is established upon the product approval by the reference state's authorized authority (expert organization).

- 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.

The Member States' authorized 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 according to the extraordinary submission procedure in accordance with paragraph 8.8.2 of these Rules.

MA holders of medicinal products, for which there are no requirements for the regular submission of a periodic safety update report, ensure that all procedures and measures provided for by these Rules are carried out to ensure continuous safety monitoring throughout the life cycle and immediately submit to the authorized authority all information that may provide influence on the assessment of the risk-benefit ratio of a product.

8.8.2. Extraordinary Submitting of a Periodic Safety Update Report.

A periodic safety update report must be submitted immediately. The preparation of a periodic safety update report should be carried out no more than 60 calendar days from the date of receipt of a written request from the Member State's authorized authority.

8.8.3. Form for Submitting a Periodic Safety Update Report Form.

A periodic safety update report must 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 authorized 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.
8.9. Evaluation Process for a Periodic Safety Update Report on the Territories of Member States

Authorized authorities of the Member States should ensure that the assessment of the periodic safety update report is carried out to determine compliance with the requirements of the right of the Union and the legislation of the Member States, as well as 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.

9. Signal Control

9.1. Structures and Processes

9.1.1. Sources of Receiving Signals and Their Processing.

9.1.1.1. 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 studies, and other information sources.

9.1.1.2. Signals from spontaneous reports can be found in individual case safety reports included in adverse reaction databases, articles from scientific literature, periodic safety update reports, or other information submitted by MA holders under procedures determined by the right of the Union and national legislation of the Member States (e.g., changes and additions, renewals, obligations for post-authorization study) or ongoing monitoring of medicinal products' risk-benefit ratio.

9.1.1.3. In many cases, signal detection results from ongoing periodic monitoring of adverse reaction databases, such as the adverse reaction databases of MA holders, authorized authorities, the World Health
Organization. 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 identify signals and stimulate the process of reporting certain types of adverse reactions by specialists.

9.1.1.4. Other sources of information include the Internet, digital media (public websites, social media, blogs), or other systems through which patients and consumers can communicate experiences of adverse drug reactions.

9.1.2. Signal Detection Methodology.

9.1.2.1. Signal detection should follow a structured and recognized 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. The signal detection procedure should take into account data from all used sources of information.

9.1.2.2. A structured and recognized methodology should be applied to assess the evidence base that supports the input signal, which should consider clinical relevance, degree of relationship validity, consistency of data, exposure-response relationship, causal link, biological plausibility, experimental results, and possibly similar in nature of the event data.


9.1.3.1. Introduction.

9.1.3.1.1. The signal processing process includes the stages from signal detection to making recommendations. Signal processing rules apply to all stakeholders involved in the safety control of authorized medicinal products.

9.1.3.1.2. Signal processing includes the following stages:
a. Signal detection.
b. Signal validation.
c. Signal prioritization.
d. Signal evaluation.
e. Recommendations for action.
f. Exchange of information.

9.1.3.1.3. The above stages of the processing process are presented in a logical sequence. Working with the individual available information sources used to detect signals may require flexibility in signal processing, in particular:

If signal detection is based on a review of individual case safety reports, the procedure may include verification and prior prioritization of the detected signal.

If a signal is detected from pooled survey results, it is generally not possible to evaluate each individual report, and additional data collection may be required as a result of validation.

Recommendations for action (followed by a decision in accordance with international treaties and acts constituting the right of the Union and the legislation of the Member States) and the exchange of information are components that need to be considered at each stage of the process.

9.1.3.2. Signal Detection.

9.1.3.2.1. The following requirements apply to all signal detection methods:

a. The method used must 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 should evaluate the cumulative data review results in a timely and appropriate manner.

e. Upon detection of a threat to public health, immediate and effective action should 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.

9.1.3.2.2. 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.

9.1.3.2.2.1. Review of individual case safety reports.

Individual case safety reports may come from spontaneous reporting, active forms of monitoring, clinical studies, or published in the medical literature. The presence of one report of a serious or severe adverse reaction (e.g., anaphylactic shock) may be sufficient to draw attention to the report and take further action. The information to be assessed should include the number of reports (after excluding duplicate reports and reports that are misrepresented), patient demographics (such as age and gender), the suspected medicinal product (such as the dose administered), and an adverse reaction (such as signs and symptoms), temporal relationship, 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 reliability of the biological and pharmacological relationship.

9.1.3.2.2.2. Statistical analyses in large databases.

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
substance or medicinal product than other active substances or products in
the database. The use of statistical methods is not suitable for 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.

The frequency of statistical analysis of the database and the formation
of a statistical report depends on the characteristics of the active substance or
medicinal product, indications, and potential or identified risks.

9.1.3.2.2.3. Combination of statistical methods and review of individual
case safety reports.

Statistical reports can be designed to identify suspected adverse
reactions that meet predefined criteria for frequency, severity, clinical
significance, novelty, or statistical relationship. Such filtering methods can
facilitate selecting the most important individual case safety reports
considered in the procedure's first step. 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, and the product use prevalence.

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 should always include a clinical evaluation. The statistical method
is an additional method for signal detection and validation.

9.1.3.3. Signal Validation.

9.1.3.3.1. When a signal is detected, an evaluation of the data is
performed to verify and confirm that the available information provides
sufficient evidence to identify a new potential causal link or a new aspect of a
previously established relationship. The validation results determine the need for further signal evaluation.

When performing the signal validation procedure, regardless of the source of its receipt, it is necessary to take into account:

9.1.3.3.1.1. Previous information on a signal:

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 substance (e.g., another 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.

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 the above are subject to validation. However, already known signals may require validation if there is a suspected difference in the incidence, duration of persistence, severity, or outcome (e.g., a fatality identified in the relationship) compared with data or characteristics included in the summary of product characteristics or previously reviewed by the Member State's authorized authority.

9.1.3.3.1.2. The level of formation of the evidence base for correlation confirmation, for example:

A total number of reports (after excluding duplicate cases), highlighting the number of reports confirming the existence of a relationship, for example, 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 an assessment of relationship by a health care professional, at least as possible, with supporting observable deviations from relevant studies.

Number of reports concerning the volume of patient exposure.

Additional reported cases of related conditions (e.g., other MedDRA terms for clinical complications or varying degrees of severity of an adverse reaction).

Consistency of the evidence base between cases (e.g., consistency in time to development, repeated observations).

Data quality and documentation.

Compliance with internationally agreed case definitions, if applicable (e.g., compliance with RegiSCAR criteria for severe skin reaction; compliance with the accepted definition of post-vaccination complications).

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 disproportionality of reporting, if applicable.

9.1.3.3.1.3. Clinical relevance and context, for example:

Seriousness and severity of the adverse reaction.

Outcome and reversibility of an adverse reaction.

New aspects of a known adverse reaction, such as 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, application error, use of an adulterated medicinal product).

9.1.3.3.1.4. Additional sources of information may contain data that will supplement the evidence base for confirming or rejecting the assumption of a new association, or a new aspect of a known association, and therefore can be used when performing the procedure for the subsequent assessment of the signal, depending on the significance and availability of this information on the institutional level of the organization performing the signal assessment. These additional sources of signal information include:

a. Clinical study data.

b. Information on the development of such cases published in the medical literature, including information on other active substances of a similar pharmacotherapeutic class of medicinal products.

c. Information on the epidemiology of adverse reactions or comorbidities.

d. Experimental and (or) non-clinical data.

e. Large adverse reaction databases in case of detection of a signal according to the databases of the authorized authority or MA holder.

f. Healthcare databases, which can be used to obtain information on patients' characteristics or the characteristics of the medicinal product use.

g. Information from regulatory authorities in other countries of the world.

9.1.3.3.2. 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 association and therefore justifies further evaluation.
9.1.3.3. A signal for which a presumably new causal link or a new aspect of a known association has not been confirmed during the validation process may require further analysis, for example, 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-authorization follow-up period should be reviewed at appropriate time intervals to ensure that all relevant reports are recorded and reviewed.

When processing a signal at the organizational 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), the need 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 amending the background information and (or) introducing risk minimization measures), or rejecting the assumption of assigning the validated signal to a new risk or an unknown aspect of a known risk (rejected signal).

9.1.3.4. MA holders and the Member States's authorized authorities should 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, and information that would assist in finding such cases and evaluating signals.

9.1.3.4. Signal Prioritization.

9.1.3.4.1. A key element of the signal management process is the immediate determination of their impact on public health or the risk-benefit
ratio of the medicinal product in exposed patients. When assessing this impact, the following factors are considered:

a. Severity, seriousness, outcome, reversibility of an adverse reaction, and the potential to prevent the adverse reaction.

b. Assessment of patient exposure and frequency of adverse reactions.

c. The degree of use of a medicinal product in vulnerable population risk groups and (or) in populations 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 other 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 minimization measures, stopping medical use, withdrawal from the market):

f. Possible signal extension to other active ingredients of the similar pharmacotherapeutic class.

9.1.3.4.2. In certain circumstances, special attention should be paid to signals that are discussed in the media or have a high level of public health significance (e.g., adverse reactions resulting from immunization of the population) to immediately communicate the results of such an assessment to the public and health care professionals.

9.1.3.4.3. The result of the signal prioritization procedure should include a recommendation on the timing of the subsequent steps 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 should be taken promptly, including until the full scope of work on signal assessment is completed. All signal handling stages should include
clinical evaluation and controls to quickly consider the information received and determine appropriate follow-up changes.

9.1.3.4.4. The result of the signal prioritization procedure must be entered into the tracking system with a justification for the assigned signal prioritization level.

9.1.3.5. Signal Evaluation.

9.1.3.5.1. The purpose of the signal evaluation is to examine further evidence of a causal link between a new risk and an active ingredient or medicinal product, or a change in a characteristic of a known risk, and 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 drug product dossier when applying for registration and subsequent changes, literature articles, spontaneous reports, and unpublished information from MA holders and the Member States' authorized 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. Aggregated information from different sources also requires the selection of internationally recognized terminology for medical events. In the absence of such a terminological definition, an operational definition is required.

9.1.3.5.2. In some cases, signals need to be assessed according to the therapeutic level or system organ class or at the standardized query level (using terms from the MedDRA dictionary). Searching for information may require the inclusion of other medicinal products of the same class and other
adverse reactions, 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).

9.1.3.5.3. Gathering information from different sources can take time. To
optimize the process, a step-by-step signal estimation method can be used,
for example. 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.

9.1.3.6. Recommendations on the actions of the Member States'
authorized authorities.

9.1.3.6.1. Recommendations based on the assessment results may vary
according to the requirements established by the acts of authorities of the
Union or the legislation of the Member States and the conclusions based on
the results of the signal assessment.

Although recommendations are made after the signal has been assessed
based on aggregate information, the need for action is assessed throughout
the signal management process, determining the rationale and feasibility of
earlier actions to minimize risk.

9.1.3.6.2. Actions based on the signal assessment results may include
additional risk assessment or risk minimization 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-authorization safety study
may be required to investigate a potential safety concern or problem.

9.1.3.6.3. If the Member State's authorized authority asks a MA holder
to take additional actions, such a request must 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. The MA holder and the Member States' authorized authorities should 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 authorization.

9.1.3.6.4. If there is no risk to patients, the Member State's authorized authority may decide that no further assessment or further action is necessary.

9.1.3.7. Exchange of Information.

9.1.3.7.1. It should be possible to exchange information between the Member States' authorized 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.

9.1.3.7.2. MA holders transmit all relevant information about signals to the Member States' authorized authorities (which is part of the obligations for pharmacovigilance and monitoring the risk-benefit ratio of the medicinal product). Validated signals that may affect public health and the risk-benefit ratio of a medicinal product must be submitted to the Member States' authorized authorities within the time frame in accordance with paragraph 9.2.3 of these Rules, and, if appropriate, proposals for possible actions should be submitted.

9.1.3.7.3. Authorized authorities of the Member States transmit the results of evaluating signals to MA holders.
9.1.3.8. Additional requirements for the process of controlling the signal of biological medicinal products.

Like other medicinal products, MA holders for biological medicinal products must 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 steps must be performed for the MA holder's biological product and concerning the active ingredient. If a signal is detected, all necessary actions should be taken to determine the cause, including identifying the suspected batch. The procedures performed should be characterized 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 should be performed throughout the entire life cycle. The clinically relevant consequences of potential immunogenicity risk (as theoretically defined for a biological medicinal product) must also be considered and monitored throughout the life cycle.

MA holders of biological medicinal products should 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 corresponding specific biological product's actual use. The process of analyzing data on actual use and detected suspected adverse reactions should be organized 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 substances may be subject to more frequent monitoring requirements; changes in the production process are grounds for special measures to ensure timely signal detection.

Signals from biological medicinal product data monitoring should 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 should be made to extend this signal to the suspected biological product or all similar active substances. 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 biological 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 should 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 to implement further measures to minimize or eliminate this risk. (e.g., optimization of control methods, stages of the production process).

9.1.4. Qualitv Requirements.

9.1.4.1. Traceabilitv.

Signal management is a critical process. Validation, prioritization, evaluation, timelines, decisions, actions, plans, reporting, and other key procedures should be properly documented and periodically monitored.
Tracking systems should also be documented and include cues that have led to the conclusion that there is no new potential causal link or a new aspect of a known relationship, as they may draw particular attention in the event of subsequent analysis. All records should be archived and retained following applicable procedures.

9.1.4.2. Quality Systems and Documentation.

9.1.4.2.1. An essential feature of the signal processing system is clear documentation to ensure the proper and efficient 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 control system should be developed following the quality system standards, which should be applied to all signal management processes. Detailed quality system procedures should be developed, documented, and implemented. This requirement applies to the methodology used and the frequency of work to identify signals. It is necessary to allocate roles and responsibilities within the company regarding actions and record-keeping, monitoring and examining quality issues, and taking corrective and preventive actions. This should also include responsibilities for quality assurance audits in the signal management system, including audits of subcontractors of the contracting parties performing any work in this area. Confidentiality of data and documentation, safety and reliability of data (including integrity during transmission) must be guaranteed.

9.1.4.2.2. The traceability system should ensure that data is retained by all parties involved during the 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.

Roles and responsibilities for completing each phase of the activity, including record keeping, quality control, review, and ensuring that corrective and preventive actions are taken, should be defined and documented.

9.1.4.2.3. A MA holder includes the description of the signal management process in the pharmacovigilance system master file. The system's efficiency in terms of this process is subject to continuous monitoring; indicators of the efficiency of the process 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 issue, 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 should ensure that regular audits are carried out, including when service providers and contract organizations are involved in this activity.

Documentation confirming the fulfillment of these requirements should be available at any time, including when necessary, to assess the feasibility and evidence-based on the actions performed and decisions made.

9.1.4.2.4. It may be necessary to review the MA holder's documentation of compliance with these provisions before and after the registration procedure to assess the activities performed or an inspection.

9.1.4.3. Training.

Personnel should be specially trained to perform signal processing activities according to assigned roles and responsibilities. The process may
include pharmacovigilance personnel and the personnel who may become aware of potential signals or involved in signal processing, such as personnel in the administrative (legal), preclinical, medical, pharmacoepidemiology, and marketing study departments. Training should include terminology and available signal source databases. Training system procedures and placement of training data should be properly documented, personnel resumes and descriptions of their roles should be archived.

9.2. Roles and Responsibilities.

9.2.1. Roles and Responsibilities of authorized authorities of the Member States.

The Member State's authorized authority performs the following actions.

Control of data on their own territory, including data obtained from other sources specified in subsection 9.1.1 of these Rules.

Validation and other stages of the procedure for processing signals received from available sources.

Submitting signals that have passed through the validation and assessment procedures to the relevant expert committees of states to determine the feasibility of subsequent actions to study further or minimize the risk.

Information sharing with other authorized authorities of the Member States about the identified signals that have been validated and the measures developed.

9.2.2. Roles and Responsibilities of MA holders.

A MA holder performs the following actions:

Continuous monitoring of the safety of medicinal products and information sharing with the Member States' authorized authorities of all new
information that may affect the conditions of approval, including emergency safety issues.

Control of all available data and information on signals.

Continuous data monitoring in adverse reaction databases and other sources of information on signals. Detection of signals should include their validation, considering the components of the information provided, specified in subsection 9.1.3.3 of these Rules.

Validation of all detected signals and reporting to the authorized authorities of the Member States.

Information sharing with the Member States' authorized authorities in case of identification of an emergency safety issue as a result of signal detection activities in accordance with paragraph 9.2.3 of these Rules;

Cooperation with the Member States' authorized authorities to implement signal assessment procedures by providing additional information upon request.

Provision of an audit trail for all signal detection procedures.

Ensuring that the medicinal product's information is consistent with the current scientific knowledge level, including the authorized authorities' new safety information assessment.

9.2.3. Emergency Safety Issues.

In case of receiving information on a medicinal product that meets the emergency safety criteria in accordance with Section I of these Rules, a MA holder ensures that the Member States' authorized authorities in whose territory the given medicinal product is authorized 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 a validated safety signal or safety concern from any source meets the definition of an emergency safety issue. The reporting
requirement for a detected emergency safety issue is in addition to the requirement for urgent submitting of individual case safety reports for cases where the emergency safety issue is based on a single case of a suspected adverse reaction.

When notifying an emergency safety issue, the MA holder should include in the submission a description of the safety concern, the source of information, any action planned or taken with a timeline, and any documentation of the safety concern available at the time of the initial notification. The MA holder shall ensure that any additional information on the safety concern is submitted to the Member States' authorized authorities as soon as it becomes available.

Upon receipt of notification of an emergency safety issue by the Member State's authorized authority, an immediate assessment of the urgency and potential impact of the safety concern is carried out, and appropriate follow-up actions and possible regulatory measures are determined concerning the identified safety concern.

The MA holder must ensure effective interaction and cooperation with the Member States' authorized authorities at the stages of assessing an emergency safety issue.

To prevent undue overload and to ensure the effectiveness of this procedure, MA holders should only report emergency safety issues that are as defined in Section I of these Rules, that is, the urgency and severity of which will not allow any delay in processing, evaluation, and acceptance of measures.

If, based on the results of an assessment of an emergency safety concern, 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 authorization or refusal to apply for confirmation of the marketing authorization, a notification of the adoption of these decisions or measures should be sent to the Member States' authorized authorities.

New safety information related to 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' authorized authorities as an emergency safety issue and is presented following the requirements and determined by the legislation of the Member States on the provision of information on deviations in the quality of a medicinal product.

9.2.4. Monitoring the Adverse Reaction Database of the Union

9.2.4.1. Order of Access to the Adverse Reaction Database

Authorized authorities of the Member States have access to all data elements of individual case safety reports, which are included in the adverse reaction database of the Union.

MA holders have access, without restriction, to all data items of individual case safety reports that have been submitted to the adverse reaction database by the MA holder himself. 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 case descriptions, with confirmation of confidentiality and use of the individual case safety report data only for signal management work.

9.2.4.2. Monitoring Frequency.

MA holders and the Member States' authorized authorities should ensure continuous monitoring of the adverse reaction database of the Union; the monitoring frequency is determined in proportion to the identified risks,
potential risks, and the need to obtain additional information on a medicinal product or active ingredient.

The frequency of monitoring data from the Union's adverse reaction database may change as data on a medicinal product's safety profile or active substance accumulates, taking into account the following factors:

- Period of time from the date of the first approval.
- The degree of exposure to patients.
- Important potential risks and missing information according to the risk management plan.
- The frequency of submission of the periodic safety update report.
- The number of individual case safety reports received during a given period.

The presence of special situations related to safety concerns (e.g., the vaccination campaign period).

MA holders should determine the appropriate monitoring frequency for each of the active substances or medicinal products to meet monitoring obligations. The minimum recommended frequency for monitoring the adverse reaction database is 6 months. More frequent monitoring is recommended for active substances 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-authorization safety study. The frequency of monitoring, including changes to be made, and the frequency justification should be documented following the organization's internal standard procedures.

9.2.4.3. Analysis of the Adverse Reaction Database of the Union.

The selection of the combination of drug and adverse reaction for the subsequent review of the data should be based on evidence-based factors such as the number of cases matched by the statistic, available data on the
safety profile of the medicinal product, clinical significance, comorbid condition, population characteristics, and data from previous assessments. Not all cases of detecting disproportionality in reporting are subject to subsequent study. On the contrary, certain identified combinations of a medicinal product and an adverse reaction, for which disproportionality in reporting has not been established, require a subsequent study to assess the adverse reaction database.

The results of the database review show information about an active ingredient or combination of active ingredients. Scientific evaluation of the data should include determining the likelihood that the signal in operation can be characteristic for all or only for certain medicinal products containing a given active substance or a combination of active substances. MA holders should include in the analysis all data on individual case safety reports that are relevant to the safety profile of the medicinal product.

When performing signal validation, analysis of the adverse reaction database data should be performed, considering the signal's prior information, the degree of evidence of the relationship, and clinical relevance. Records management for monitoring and analyzing the database is performed following the organization's internal standard procedures.

9.2.5. The procedure for notifying the Member States' authorized authorities by the holders of the marketing authorization of the signals detected based on monitoring the adverse reaction database of the Union.

If a new signal is detected during monitoring of the adverse reaction database of the Union, a MA holder must validate this signal and then inform the Member States' authorized authorities.

Signal validation should include careful analysis by the marketing authorization database of the adverse reaction database; for validated signals, the analysis should be complemented by assessing other available relevant
data (e.g., marketing authorization database, literature, clinical study data). The MA holder, if possible, should assess the distribution of information about the established new risk to other medicinal products containing a similar active ingredient (except for cases of identifying a risk related to a specific medicinal product); in this case, the information on the medicinal product should be brought into line with the newly identified risk by amending the conditions of the marketing authorization. The MA holder should also consider the information regarding signals published or under consideration by the Member States' authorized authorities.

Based on his own assessment, the MA holder can make the following conclusions regarding the signal:

- Signal can be classified as rejected.
- Signal is a new risk.
- Signal represents a change in a previously known risk.
- Signal evaluation requiring a subsequent analysis and carried out by the authorized authorities.

The conclusion that the signal is a new or changed risk and (or) that further analysis is required to be carried out by the authorized authorities is the starting point (“Day 0”) of the signal notification periods specified in this document.

The establishment of a new or changed risk, which requires a change in the marketing authorization conditions, is the basis for applying to changing the conditions of the marketing authorization if the MA holder does not believe that the subsequent analysis of the signal by the authorized authorities is justified. Subsequent analysis by the authorized 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.
Informing about signals requiring further analysis by the authorized authorities can only be carried out within the framework of a periodic safety update report if the conditions specified in paragraph 9.2.5.2 of these Rules are met. If the conditions of paragraph 9.2.5.2 are not met, the MA holder must send a separate notification of the signal to the Member States' authorized authorities in accordance with paragraph 9.2.5.3 of these Rules.

Notification of rejected signals to the Member States' authorized authorities is carried out only through the inclusion of this information in the periodic safety update report.

Informing the Member States' authorized authorities about validated signals requiring immediate attention is carried out as part of the procedure for notification of an emergency safety issue in accordance with paragraph 9.2.3 of these Rules.

9.2.5.1. Changing the Conditions of the Marketing Authorization

Based on his own assessment of the detected signal when monitoring the adverse reaction database, the MA holder can conclude the need to bring the information about the medicinal product and (or) the risk management plan in line with the new data by making changes. In such cases, the MA holder should submit to the relevant authorized authorities an application for amending the conditions of the marketing authorization as soon as possible, but no later than after 3 months after the completion of the signal assessment, according to the results of which the signal is assessed as meeting the definition of an important risk, or within 6 months in the case of adverse reactions or risks that are not considered important.

In these cases, a separate notification of the signal in accordance with paragraph 9.2.5.3 of these Rules is not required since the proposed changes, and the authorized authorities will assess the corresponding evidence base as
part of the procedure for amending the conditions of the marketing authorization.

MA holders should comply with the recommendations of the current legislation in terms of amending the conditions of the marketing authorization and, in appropriate cases, coordinate with the authorized authorities issues related to the preparation of an application for amendments.

9.2.5.2. Include a Signal in a Periodic Safety Update Report

If the frequency of submission of a periodic safety update report for the corresponding active ingredient of a medicinal product is 6 months after the completion of the assessment by the MA holder of the signal identified as a result of continuous monitoring of the adverse reaction database, submission of a separate notification of the signal to the Member State's authorized authority in accordance with paragraph 9.2.5.3 of these Rules is not required. If 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 After the Completion of the Preparation of the Periodic Safety Update Report” along with the proposal for further signal management.

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 amend the conditions of the marketing authorization and (or) take action, including any changes to the approved medicinal product information for the product for which the periodic safety report update has been submitted. This also applies to conclusions based on the assessment of safety signals.

Regardless of the source of information on the signal, the periodic safety update report includes information on all validated alarms and
emergency safety issues that were assessed during the reporting period of the periodic safety update report or after the closure of the databases.

9.2.5.3. Special Signal Notification

If a MA holder, based on the performed assessment of the signal detected by monitoring the adverse reactions database, concludes that this signal does not comply with the requirements of paragraphs 9.2.5.1 and 9.2.5.2 of these Rules and the need for subsequent analysis of the signal by the Member States' authorized authorities, the MA holder should fill out the special signal notification form available on the web portal of the Member States' authorized authorities and send the notification form to the Member States' authorized authorities of in which the corresponding medicinal product is approved.

Special notification of the signal should be sent as soon as possible, but no later than after 30 calendar days after the MA holder has completed the assessment and concluded the need for analysis by the Member States' authorized authorities.

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 amending the conditions of the marketing authorization in accordance with the provisions of paragraphs 9.2.5.1 and 9.2.5.2 of these Rules.

Information on signals that, based on the assessment, were rejected by the holders of the marketing authorization should not be sent to the Member States' authorized authorities in the form of special notifications about the signal. Still, information on these signals should be included in the periodic safety update report.

9.2.3. Subsequent Regulatory Processes.
If the Member States' authorized authority decides on the need for additional actions, the signal is assessed, and subsequent actions concerning the marketing authorization are agreed upon within a time frame corresponding with the degree and severity of the safety concern. The following decisions may be made based on the results of the procedures:

- MA holder must provide additional data for the assessment as part of the procedure being performed.
- MA holder must conduct an additional assessment of the data and submit such an assessment following the established time frames.
- MA holder must review the additional data on the signal as part of the next or unscheduled periodic safety update report.
- MA holder must bring the medicinal product information in line with the new information to amend the approval conditions.
- MA holder must finance the post-authorization study following the agreed protocol and provide the final results of such a study.
- MA holder must submit a risk management plan or an updated version of the indicated plan according to the new information.
- MA holder must take additional risk minimization measures required to ensure the safe and effective use of a medicinal product, for example, carry out an educational program or direct information to health care professionals.

The approval status is subject to change, the marketing authorization must be suspended, withdrawn, or not renewed.

- Urgent safety restrictions must be imposed.
- Authorized 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.
- Authorized authorities of the Member States need to obtain additional scientific advice 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 acts of authorities of the Union and the legislation of the Member States.

It is necessary to include the suspected medicinal product in the list of products subject to additional monitoring.

It is necessary to perform other additional actions not mentioned above.

No additional assessment or action beyond routine pharmacovigilance is required.

Recommendations of the Member States' authorized authorities based on the assessment results of signals are subject to publication on the Member States' authorized authorities' official web portal.

9.2.4. Management of Records in the Safety Concern Tracking System of the Member States' authorized authorities

The Member States' authorized authorities ensure that information is entered into the system for tracking safety concerns of the Member States' authorized authorities according to the following signals:

Signals in respect of which the Member State's authorized authority carried out the validation procedure.

Validated signals, information about which was received from MA holders.

Emergency safety issues.

Information on signals in the system for tracking safety concerns of the Member States' authorized authorities includes the following elements:

Description of the validated signal.

For rejected signals: basis for rejection.

For confirmed signals: a report on the evaluation of signals, the timing of the steps of the procedures, the recommendations of the expert committee.
9.2.5. Openness.

Member States should monitor the timeliness of communication to the public of important safety concerns identified by the pharmacovigilance system through publication on the web portal and other available means of communication.


10.1. Introduction

A post-authorization safety study of a medicinal product may be initiated, controlled, or financed by the MA holder voluntarily or in accordance with the obligation imposed on him by the authorized authority of the Member States as a condition for issuing a marketing authorization or after the issuance of marketing authorization, if there is an assumption that there are risks associated with the authorized medicinal product requiring additional study by conducting a study.

A post-authorization safety study can be a clinical study or a non-interventional study.

10.2. Structures and Processes

10.2.1. Scope.

This section's requirements apply to non-interventional post-authorization safety studies initiated, controlled, or funded by the MA holder in the territory of the Member States voluntarily or following the obligations imposed on him by the Member States' authorized authorities. A post-authorization safety study includes a study that collects data from patients and healthcare workers and studies that reuse data previously obtained for
another purpose and stored in patients' medical records or other storage data (including electronic forms).

If the post-authorization safety study is a clinical trial, it must comply with the requirements stipulated by the acts of authorities of the Union and the legislation of the Member States for the organization and conduct of clinical studies.

10.3. Terminology

This section uses the following terms, which mean the following:

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

“End of data collection” is the date when the analytical database is first fully available.

“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.

“Start of data collection” is the date of registration of data on the first patient included in the study, in the form (database) of data collection of the study, or case of reuse of data is the date of the start of data retrieval.

“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, such as 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 impact, the outcomes and combination variables in the statistical data analysis plan defined by the study protocol.

10.4. Structures and Processes
10.4.1. General Principles

A non-interventional post-authorization safety study's primary objective should be to obtain scientific evidence of potential clinical or public health significance.

The objectives of a post-authorization safety study may include.

Quantifying potential or identified risks, for example, assessing the frequency of occurrence, relative risks compared to a population that has not used a given medicinal product or a population that has used another drug or class of drugs, as well as examining risk factors and factors that modify the effect of a product.

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-marketing stage (e.g., pregnant women, special age groups, patients with renal or hepatic impairment).

Assessment of the risk associated with long-term use of a medicinal product.

Confirmation of the absence of risks of medicinal products.

Assessment of the standard medical practice of prescribing medicinal products with obtaining additional information on the safety of products or the effectiveness of risk minimization measures (e.g., collection of information on use according to indications, use not following the summary of product characteristics, prescribed dosages, 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).

Assessment of the effectiveness of risk minimization measures.

The design of a post-authorization safety study should correspond to the purpose of the study. In contrast, a study's classification as a post-
authorization study is not limited to the type of design chosen if it meets the above criteria. For example, a systematic literature review or meta-analysis may be considered a post-authorization safety study depending on the studies' objectives.

MA holders should consider the relevant scientific guidelines in developing study protocols, conducting the study, and compiling study reports. To assess study protocols and study reports, the Member States' authorized authorities should consider the current versions of the applicable scientific guidelines and methodological standards for pharmacoepidemiology.

For post-authorization safety studies sponsored by the MA holder and developed, conducted, and analyzed in whole or in part by investigators other than the marketing author's employees, the MA holder must ensure that the investigators have the necessary education and training, and experience qualifications to carry out their duties.

The agreement concluded between the MA holder, and the investigators must ensure the fulfillment of the study's regulatory obligations and the scientific examination of the data obtained. In the agreement, the MA holder should provide for the conditions that determine the implementation of methodological standards for conducting pharmacoepidemiological studies and reflect the following aspects of the study's organization and conduct:

Rationale, main objectives, and a summary of the planned study methods performed by the investigator.

Rights and obligations of the investigator and the MA holder.

Determination of the tasks and responsibilities of the parties.

Procedure for obtaining agreement on the study protocol.
Procedures to ensure that the MA holder fulfills its pharmacovigilance obligations, including urgent reporting of adverse reactions and other safety data by investigators, if applicable.

Intellectual property rights arising from study and access to study results.

Storage and access to the data set for analysis and the statistical programs used to process the data for auditing and inspecting the study.

A strategy for informing about the stages of the study and the preparation of the final report.

A strategy for publishing interim and final study results.

A non-interventional post-authorization study should 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-party personnel engaged by the MA holder to conduct the research.

Paying health care professionals to participate in a study should be limited to reimbursement of the time and cost required to complete the study.

10.4.2. Study Approval.

Non-interventional post-authorization safety studies, the conduct of which is part of the MA holder's obligations established by the Member State's authorized authority, are subject to registration in the electronic register of post-authorization studies of the Member States (hereinafter referred to as the register) posted on the web portal of the relevant the Member State's authorized authority. The date of registration of the post-authorization study in the electronic registry is taken as the key date concerning submitting the final report on the study results.
To ensure transparency concerning all non-interventional studies performed, as well as the exchange of pharmacovigilance data between the Member State's authorized authorities and MA holders, MA holders should ensure that all non-interventional post-authorization safety studies provided for by risk management plans agreed with the Member State's authorized authorities or performed voluntarily are included in the registry of post-authorization studies.

Non-interventional post-authorization studies are subject to registration in the register before starting the study, or as soon as possible, for example, if data collection within the study agreed in the risk management plan has been started. The study protocol is to be included in the registry at the earliest possible date and before the study data collection. Significant changes to the protocol, reports on the study's progress, and the final report of the study must be included in the registry as soon as possible, but no later than 14 calendar days after completing the preparation of these documents. Information on the study is presented preferably in Russian. If the study protocol is written 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.

If the prior placement of the protocol in the registry may adversely affect the validity of the study (e.g., in studies with initial data collection, for which prior availability of information regarding study objectives may lead to data errors) or protection of intellectual rights, a revised study protocol may be entered in the registry by the MA holder before data collection begins. This revision of the protocol should be reasonable and the minimum necessary for the editing process. The title page of the protocol should include the indication “Protocol Revision.” In this case, before the start of data collection, the complete study protocol is provided by the MA holder at
the request of the Member State's authorized authority. The complete study protocol must be placed in the registry as soon as possible after the end of data collection, but no later than 14 calendar days.

10.5. Study Protocol.

Non-interventional post-authorization safety studies performed by MA holders following obligations imposed by authorized authorities or voluntarily should have a written study protocol. All post-authorization safety studies should be performed according to a scientifically sound study protocol developed by individuals with appropriate scientific training and experience.

For voluntarily initiated post-authorization safety studies, the MA holder is advised to submit the study protocol before the start of data collection to the Member State's authorized authority, on the territory of which it is planned to conduct a post-authorization non-interventional safety study of a medicinal product.

For post-authorization safety studies initiated by the MA holder following the obligation imposed by the authorized authority of the Member State, the MA holder must ensure that information about the research, including the draft study protocol, is submitted to the Member State's authorized authority, which has been obliged to conduct post-authorization safety studies before data collection. In the case of post-authorization safety studies on the territory of other Member States, it is necessary to inform the authorized authorities of these states of the study protocol submission.

For the MA holder to fulfill his obligations to carry out pharmacovigilance activities, the pharmacovigilance officer, or the person to whom the relevant powers have been delegated, should be involved in the review and approval of study protocols carried out following the obligations under the agreed risk management plan, or voluntarily. The national
pharmacovigilance focal point must be informed of any post-authorization safety study conducted or sponsored by the MA holder in the Member State concerned. It must have access to the study protocol.

10.5.1. Format and Content of the Test Report.

The post-authorization safety study protocol, which is part of the obligations or the agreed risk management plan of the MA holder and carried out voluntarily, should contain the following sections:

10.5.1.1. Name of post-authorization safety studies: informative name, including commonly used terminology, defining the study design and the investigational medicinal product, the active substance or group of the investigational product, and a subtitle indicating the edition and the date of the last revision. After approval of the study protocol in the registry, subsequent versions must contain the number of post-authorization safety studies according to the registration number in the registry.

10.5.1.2. MA holder: Name and Address of the MA Holder.

10.5.1.3. Responsible parties: names, titles, qualifications, addresses, and details of all responsible parties, including the main author of the protocol, principal investigators, study coordinators for each country and study sites in which the study is to be carried out, and other information related to the study sites. A list of all institutions and researchers involved in the study should be available upon request from the Member States' authorized authorities.

10.5.1.4. Summary: A separate summary of the study protocol, including the following subsections:

- Name of the study with subtitles, including the revision version and date of the protocol, and the name and information about the main place of work of the main author of the protocol.

- Rationale and prerequisites for conducting.
Objective and objectives of the study.
Study design.
Study population.
Monitored indicators.
Data sources.
Study size (sample size).
Data analysis.
Main steps.

10.5.1.5. Changes and Updates: Any significant change and update to the test report after the start of data collection, including the rationale for each change or update, the dates of each change, and a link to the section of the changed protocol.

10.5.1.6. Main Steps: Data in tabular form with planned dates for implementing the study's following main steps:
   - Start of data collection.
   - End of data collection.
   - Study progress reports.
   - Interim reports on the study results, if applicable, following the steps of data analysis.
   - Final report on the study results.
   - Data should be provided for any other important steps in the study.

10.5.1.7. Rationale and Background: Description of the safety concern(s), safety profile, or risk management measures that led to the initiation of 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 information that the study is designed to obtain. The review may include results from relevant animal experiments, clinical studies, population statistics, and data from previous epidemiological studies.
The review should contain references to the results of similar studies and the expected contribution of this study.

10.5.1.8 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 should be obtained in the study.

10.5.1.9. Study Methods: description of study methods that include the following:

10.5.1.9.1. Study Design: Description of the study design and the rationale for its selection.

10.5.1.9.2. Conditions: Study population, defined in terms of person, place, time period, and sampling criteria, including the rationale 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.

10.5.1.9.3. Variables: outcomes, impacts, and other variables, including measurable risk factors, should be described with a characterization of each separately; potential factors that distort outcomes and factors that modify effects, including operational definitions, should be specified.

10.5.1.9.4. 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 must 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.

10.5.1.9.5. 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.

10.5.1.9.6. Data Management: Data management and statistical software used in the study, including procedures for collecting, recovering, and preparing data.

10.5.1.9.7. Data Analysis: All the critical steps from raw data to final output, including 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 should be clearly distinguished from subgroup analysis and secondary analysis.

10.5.1.9.8. Quality Control: Description of the mechanisms and procedures to ensure the quality and integrity of data, including the accuracy and readability of the data obtained and primary documentation, the storage of records and archiving of statistical programs, a description of the data available for the validation of the procedures for the verification of records and the validation of endpoints. Includes certification and (or) qualifications for any supporting laboratory or study groups (if applicable).
10.5.1.9.9. Limitations of Study Methods: Any potential limitations of study design, data sources, and analytical methods, including problems of bias, bias, generalization, and random error. There is a need to discuss the likelihood of success of measures to reduce errors.

10.5.1.10. Protecting Study Subjects: Safety measures to ensure compliance with a Member State's legislation on the welfare and rights of participants in non-interventional post-authorization safety studies.

10.5.1.11. Data Management and Reporting of Adverse Events and Adverse Reactions: Procedures for 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.

For studies involving the primary collection of data, if certain adverse events are excluded from the volume of data collected, the MA holder should justify the approach to safety data collection used in this post-authorization safety study in the study protocol. The indication of adverse events excluded from the collected data should 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 health care professionals and patients should include the contact details of the MA holder or the authorized authority and special forms designed to submit information on adverse reactions. Under certain circumstances, in the case where a suspected fatal adverse reaction is not subject to immediate reporting in the form of an individual report of an adverse reaction, each of these reactions should be included in a list indicating the appropriate level of the MedDRA dictionary and giving reasons for excluding these cases from the urgent reporting procedure.
For studies based on the collection of secondary data, this part should indicate the analyzed 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.

When performing a study with a combined design, the requirements for studies based on primary data collection must be applied to adverse reactions for which information is obtained through primary data collection, and the requirements for studies based on secondary data collection must be applied to adverse reactions for which information is obtained through secondary data collection.

10.5.1.12. Plans for distributing the findings and communicating the study results, including plans for submitting ongoing reports, final reports, and publications.

10.5.1.13. References.

The section can include any additional or auxiliary information about specific aspects that were not previously considered (e.g., questionnaires, reporting forms).

Feasibility studies conducted to validate protocol development, such as testing questionnaires or simple calculations of medical events or prescriptions from a database to determine the study's statistical accuracy, should be posted in the appropriate section of the study protocol with a summary of the methods and results. The MA holder must submit full reports at the request of the Member State's authorized authority. Feasibility studies that are part of the study process should be fully described in the protocol (e.g., pilot evaluation of the patient questionnaire used).

10.5.2. Control over Changes to the Study Protocol.
Changes and updates to the study protocol should be carried out as needed during the study. Any significant changes to the protocol after the start of the study should be recorded in the protocol so that it can be tracked and verified, including the dates of changes. If the amendments to the protocol led to the study being recognized as an interventional clinical study, then the study is carried out following international treaties and acts constituting the right of the Union and the legislation of the Member States.

For voluntarily initiated post-authorization safety studies, the MA holder is recommended to transfer the study protocol with changes or updates to the Member State's authorized authority, on the territory of which the post-authorization non-interventional safety study of a medicinal product is being conducted.

For post-authorization safety studies initiated by the MA holder following the obligation imposed by the Member State's authorized authority, the MA holder must provide information on the introduction of any significant changes to the study protocol to the Member State's authorized authority, which were obliged to conduct post-authorization safety studies before their introduction.

10.6. Submission of pharmacovigilance data to authorized authorities of the Member States.

10.6.1. Data that are Significant for Assessing the Risk-benefit Ratio of a Medicinal Product.

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' authorized authorities, in whose territory the post-authorization safety study is conducted and the investigational product is authorized, in the form of an
emergency 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.

This communication should not affect the information on study results provided as part of the periodic safety update report and in the risk management plan's updates (if applicable).

10.6.2. Suspected Adverse Reactions and Adverse Events That Should Be Reported Urgently.

Information on serious unforeseen adverse reactions should be submitted urgently to the Member States' authorized authorities in accordance with the requirements of Section VII of these Rules.

Information on adverse reactions and adverse events collected during primary data collection studies should be documented and summarized in the interim safety data analysis report and the final study report.

Information on adverse reactions and adverse events collected during studies with secondary data collection shall be documented and summarized 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.

Procedures for collecting adverse reaction information, managing data (including review and evaluation by the MA holder, if applicable), and reporting suspected adverse reactions should be performed at the clinical study site. They should be summarized in the study protocol.

10.6.3. Study Reports.

The study progress report is intended to include relevant information that reflects 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.

The study interim report is intended to include the planned interim analysis of study data before or after the end of data collection.

The Member State's authorized authority may request the submission of a report on the progress of the study on the ongoing post-authorization safety study, which is part of the MA holder's obligations or is carried out voluntarily in the territory of the Member State. Requests for study progress reports may be made before the start of the study or at any time 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 in the context of regulatory procedures and important safety information on a medicinal product.

The time for submission of interim reports should be agreed upon with the Member States' authorized authorities and indicated in the study protocol in case of agreement on the procedure for submitting reports before the start of the study. The post-authorization safety study's progress should be reflected appropriately in a periodic safety update report and risk management plan updates (if applicable).

After considering the report by the Member State's authorized authority, additional information may be requested.

10.6.3.2. Final Study Report.

The final report of a non-interventional post-authorization safety study initiated by a MA holder according to an obligation imposed by the Member
State's authorized authority shall be submitted with the Member State's authorized authorities as soon as possible after its completion and within 12 months of the date of completion of data collection.

For post-authorization safety studies voluntarily initiated by the MA holder, it is also recommended to submit the final study report to the Member States' authorized authorities where a medicinal product is approved.

In case of stopping the study, a final report is submitted explaining the reason for stopping the study.

The final report of the post-authorization safety study should include the following sections and information:

10.6.3.2.1. Title: A title that includes common terminology and indicates the study design, subheadings with the date of the final report, the name, and information about the main author of the report. If the study was authorized in the registry of post-authorization safety studies of the Member States, the registration number and a link to the posted records of the study on the web portal of the Member States' authorized authorities should be indicated.

10.6.3.2.2. Executive Summary: A separate summary in the format below.

10.6.3.2.3. MA holder: Name and address of a MA holder.

10.6.3.2.4. Researchers: names, titles, degrees, addresses, and details of all researchers, and a list of all organizations and locations involved in the study. This information should be provided for each country and study site in which the study was carried out and other information relevant to the study's location. A list of all institutions and researchers involved in the study should be available upon request from the Member States' authorized authorities.

10.6.3.2.5. Control points (dates for the following control points for the study):
Start of data collection (planned and actual).

End of data collection (planned and actual) or date of early termination, if applicable, indicating the reasons for early termination.

Reporting on the progress of the study.

Interim reporting of study results (if applicable).

Final report on the results of the study.

Any other important control points applicable to the study, including the date of approval of the protocol by the ethics committee (if applicable) and the date of the study approval in the electronic study registry.

10.6.3.2.6. Rationale and background for the study: a description of the safety concern that led to the study's initiation 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 as designed to acquire.

10.6.3.2.7. Study Purpose and Objectives: The study's purpose and objectives, including any preliminary hypotheses, following the test protocol.

10.6.3.2.8. Changes and Updates: A list of any significant changes and updates to the original test report since the start of data collection, including the rationale for each change or update.

10.6.3.2.9. Study methods, including the following:

Study design: Key elements of the study design and the rationale 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 rationale.

Patients: any target population and criteria for enrolling patients in the study. Sources and methods of selection of participants should be indicated,
including (where applicable) methods of individualization of cases and the number and reasons for exclusion from the study.

Variables: all outcomes, impacts, prognostic factors, potential confounding, and effect-modifying factors, including operational definitions and diagnostic criteria, if applicable.

Data Sources and Measurement: For each variable 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 are available) are indicated. If the study used an existing data source such as electronic health records, any information about the records' validity and the coding of the data should be provided. 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 any processes for obtaining and confirming data from investigators should 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 rationale 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 rationale of the selected methods of grouping data.

Statistical methods (description by the following aspects):
Basic methods of generalization.
All statistical methods used in the study, including methods for controlling bias and, concerning meta-analyzes, 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 sensitivity of the study.

All changes to the data analysis plan provided for by the study protocol, with the rationale for the changes.

Quality Control: Mechanisms and procedures to ensure the quality and integrity of data.

10.6.3.2.10. Results: Presentation of tables, graphs, and illustrations to display the data obtained and the analysis performed. Both adapted and non-adapted results should be presented. The assessment of the accuracy of the data should be performed quantitatively with confidence intervals. This section should include the following subsections:

a) Participants: Number of patients at each stage of the study (e.g., number of potentially eligible, screened, confirmed as eligible, enrolled, completed, and reviewed, and reasons for dropping out of the study at any stage). In the case of a systematic review or meta-analysis- number of studies screened, assessed for relevance, and included in the review, indicating the reasons for exclusion at each stage.

б) Descriptive Data: Characteristics of study participants, information on exposure and potential confounding factors, and the number of participants with missing data for each variable under consideration. In the case of a systematic review or meta-analysis, characteristics of each study whose data were used (e.g., sample size, follow-up).

в) Results Data: Number of participants by main result category.

g) Key results: Unadapted evaluation results (if applicable), the adjusted estimate for confounding factors, and their accuracy (e.g., 95% confidence interval). If applicable, the relative risk evaluation should be translated into absolute risk for a significant period of time.

d) Other Analyses: Other analyzes performed, such as subgroup and interaction analyzes and sensitivity analyzes.
e) Adverse events and adverse reactions: data management and reporting of adverse events and adverse reactions to the Member States' authorized authorities in accordance with the requirements of Section VII of these Rules. For certain study designs, such as case–control or retrospective cohort studies, especially those involving analysis of electronic health record data, systematic reviews, and meta-analyses, it should be stated that it is impossible to make estimates of the reliability of the causal link at the individual case level.

10.6.3.2.11. Discussion:

a) Key Results: Key results relevant to the study's objectives, previously conducted study, the results of which are consistent with or inconsistent with current results, the effect of the results on the risk-benefit ratio of the medicinal product, if applicable.

б) Limitations: Limitations of the study, considering 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. Discussion is needed on both the direction and the scale of potential errors.

в) Interpretation: Interpretation of study results considering objectives, restrictions, multiple analyzes, results from similar studies, and other relevant evidence.

г) Generalizability (external validity of study results).

10.6.3.2.12. Links.

10.6.3.2.13. Other Information: Any additional or supporting information about specific aspects of the study not previously considered.
10.6.3.3. The summary of the study's final report should include summarized information about the methods and results of the study, presented in the following format:

a. Title with subheadings, including the date of the summary, name, and details of the first author.

b. Keywords (no more than 5 keywords reflecting the main characteristics of the study).

c. Rationale and prerequisites.

d. Objective and objectives of the study.

e. Study design.

f. Conditions.

g. Patients and sample size.

h. Variables and data sources.

i. Results.

j. Discussion (including, if applicable, an assessment of the study's effect on the risk-benefit ratio of a medicinal product).

k. Conclusion.

l. MA holder.

m. Name and details of the principal investigator.

10.7. Publication of Study Results by the Authors.

A MA holder is advised to agree in advance on the publication strategy with a principal investigator if the study is conducted and analyzed in whole or in part by investigators who are not part of the MA holder. The MA holder should be authorized to review the results and their interpretation in the script and submit comments before the script is submitted for publication, avoiding unreasonable delays in publication. Requests for changes to the script must be scientifically based.
10.7.1. Submission of Published Study Results to authorized authorities of the Member States.

To enable the authorized authority to review and interpret the study data planned for publication in advance, a MA holder is recommended to submit the final script of the article to the Member States' authorized authorities in whose territory a medicinal product is authorized within 14 calendar days from the date of receipt of the publication at the publishing house.

10.8. Data Protection

MA holders and investigators must comply with the legislation of the Member States in which the study is being conducted to protect the privacy of patients. A MA holder must ensure that all study information is handled and stored so that it can be accurately reported, interpreted, and verified. At the same time, the confidentiality of patient medical records should not be violated.

10.9. Quality Systems, Audits, and Inspections

A MA holder must ensure that his pharmacovigilance obligations are met concerning the study and provide the possibility of auditing, inspection, and verifying this activity. Any change in data should be recorded to ensure traceability. The MA holder must ensure that the analytical datasets and statistical programs used to generate the final study report's data are electronically stored and made available for audit and inspection.

10.10. Impact on the Risk Management System
Non-interventional post-authorization safety studies (and, in general, any interventional or non-interventional post-authorization safety studies) conducted to investigate safety concerns as described in the risk management plan should be included in the plan. The study protocol should accompany the risk management plan.

If there is no risk management plan, a new plan should be developed, including the post-authorization safety study data. All relevant sections and modules of the risk management plan are amended accordingly to reflect the study, including the safety data sheet, pharmacovigilance plan and risk minimization plan, and an overview of risk minimization measures.

10.11. Procedure for Mandatory Post-Authorization Safety Studies

In the Member States, a post-authorization safety study may be mandatory when evaluating the initial application for state registration or at the post-marketing stage if there is a concern (a reasonable expert opinion regarding the lack of important data characterizing the safety profile of a medicinal product, the receipt of which requires the implementation of active methods of safety studies according to due to the inability to properly study or assess the risk (risks) using routine pharmacovigilance methods) concerning the safety profile of the authorized medicinal product. This requirement of the authorized authority must be properly justified by the data of the assessment of the safety and efficacy profile, must be recorded in writing, and must include the objectives and time frames for the study's submission and conduct. The requirement may also include recommendations for the study's key characteristics (e.g., study design, conditions, exposure, 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 studies, consumption studies, pharmacoepidemiological studies.

Within 30 calendar days after receiving written notification from the authorized authorities about the appointment of a post-authorization safety study at the post-marketing 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. Authorized authorities of the Member States determine the period for which the indicated comments are submitted. Based on the analysis of these written comments submitted by the MA holder, the Member State's authorized authority must withdraw or confirm the obligation. If the obligation is confirmed, the conditions for issuing a marketing authorization must be amended accordingly, defining a post-authorization safety study as an approval condition. If there is a risk management plan, the MA holder changes the relevant sections of the plan.


10.12.1. Role and Responsibilities of MA holders.

A MA holder is responsible for ensuring that the study meets the criteria for a non-interventional study.

The MA holder for the post-authorization safety study must ensure that its pharmacovigilance obligations are met and that it can be audited, reviewed, and verified.

When the MA holder is obliged to conduct a non-interventional post-authorization safety study, the MA holder must ensure the development of the study protocol with subsequent submission for assessment to the Member
State's authorized 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.

A post-authorization safety study can be started only after receiving written approval from the Member State's authorized authority in whose territory the study is planned to be carried out. Approval by the authorized authority should be based on ensuring the well-being and protection of study participants' rights.

After agreeing on the protocol, the MA holder must ensure that all subsequent planned significant changes to the post-authorization safety study protocol are submitted to the authorized authority before the start of their introduction.

Upon completion of the study, the MA holder submits the final report on the study, including the summary of the study for publication, to the authorized authority of the Member State as soon as possible, but no later than 365 calendar days (12 months) after the end of data collection, if the Member State's authorized 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 authorized authority no later than 3 months before the deadline for the mandatory report submission.

The MA holder is responsible for carrying out a proper assessment of the study results, the impact of the results on the conditions of approval, and submission, if necessary, to the Member States' authorized authorities of an application for amending approval conditions.

10.12.2. Authorized authorities of the Member States.

After receiving the authorized authorities' decision on the appointment of a non-interventional post-authorization safety study, the MA holder develops a
study protocol and submits it to the Member State's authorized authority for consideration. Within 60 calendar days from the date of submission of the draft protocol, the Member State's authorized authority prepares a response regarding:

- Approval of the draft study protocol.
- Recommendations for amending the study protocol.
- Refusal to agree on the study protocol.
- Notifying the MA holder that the study is a clinical study subject to the requirements of international treaties and acts that constitute the right of the Union and the legislation of the Member State in the field of clinical studies.

The refusal must include a detailed rationale of the reasons for the non-conformity in any of the following cases:

- If there is reason to believe that the study contributes to the marketing promotion of a medicinal product.
- If 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 authorized authority.

After the study starts, any significant changes to the protocol are submitted to the Member State's authorized authority before their introduction. The Member State's authorized authority within 60 calendar days after the submission of changes to the study plan must evaluate these changes and inform the MA holder about their approval or rejection. In case of rejection of the changes made to the protocol, the written opinion of the Member State's authorized authority must include an indication of the time period for re-submission of changes to the study protocol.

Authorized authorities of the Member States ensure the exchange of information on the results of the post-authorization safety study protocols
assessment regarding medicinal products that are authorized in the territory of other Member States.

Upon completing the study, the MA holder submits the final study report, including the summary of the study for publication, to the Member State's authorized authority. 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 authorized authority should determine the need for recommendations on amending the registration status of the medicinal product, its use, or determine the need for 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 should be taken after the interim report's evaluation if important safety data of a medicinal product are identified at the interim data evaluation stage.

11. Safety Information Sharing

11.1. Structures and Processes


Safety information sharing aims to:

a. Submission of timely, scientifically-based information on the safe and effective use of medicinal products.

b. Assistance in the optimization of medical practice (including the practice of self-medication), if necessary.

c. Change in approaches, established practice, and the nature of the use of medicinal products.

d. Support of activities related to risk minimization.
e) Assistance in making informed decisions on the rational use of medicinal products.

In addition to the above, proper safety information helps build public confidence in the regulatory system.

11.1.2. Safety Information Sharing Principles.

The following safety information sharing principles should be applied:

a. The need for safety information sharing is considered when performing pharmacovigilance and risk management activities. This component should be part of the risk assessment process.

b. The need to ensure proper coordination of activities and interaction between the various parties involved in creating and exchanging safety information (authorized authorities of the Member States, other state authorities, and MA holders).

c. 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.

d. The need to adapt safety information by using the appropriate language and considering different levels of knowledge and information needs for different target audiences (e.g., patients and healthcare workers), provided that the information transmitted is accurate and consistent.

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, severity, frequency of adverse reactions, risk factors for their development, time of onset, reversibility and, if possible, the expected recovery period.

f. Safety information sharing should help to resolve uncertainties in safety data. This is especially true in new information emerging when the Member States' authorized authorities carry out the safety data assessment
procedures. The benefits of communicating at this stage should be weighed against the risk of an error that could arise if the profile's uncertain aspects were not adequately explained.

g. In certain cases, when reporting safety information, it is necessary to consider competing risks (e.g., the risk of refusing treatment).

h. The need to use the most reasonable quantitative indicators when describing and comparing risks (e.g., an indicator of relative risks and absolute risks). To compare risks, the groups should 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 counseling or testing of medical workers or patients to prepare safety information, especially when preparing information on difficult concerns.

j. Safety information sharing should include the submission of follow-up information (e.g., subsequent changes to recommendations, resolution of the safety concern) (if necessary).

k. Assessing the efficacy of safety information sharing (if necessary and possible).

l. Compliance of safety information with the requirements for the protection of personal data.

11.1.3. Target Audiences.

The main target audiences for safety information sharing by Member State's authorized authorities and MA holders are health care professionals, patients, and caregivers who use medicinal products (i.e., prescribe, prescribe, dispense, participate in turnover, enter or accept).

Health care 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.

Patients, consumers, and health care professionals can play an important role in distributing important safety reports to their intended target audiences.

The media is also the target audience for safety information. The media's ability to reach patients, health care professionals, and the general public is an important factor in distributing new and important medicinal product information. Safety information distribution through the media impacts public perception; therefore, the media need to receive safety information directly from the Member States' authorized authorities and the information they receive from other sources (e.g., from the MA holders).

11.1.4. Safety Information Content.

The information distributed during the safety information sharing must be objective and must not be misleading.

Taking into account the principles set out in subparagraph 11.1.2 of these Rules; the safety information must contain:

a. Emerging important information about any authorized medicinal product that affects the risk-benefit ratio of a medicinal product under any conditions of use.

b. The reasons for initiating the safety information sharing procedure in a form understandable to the target audience.

c. Necessary recommendations to health care professionals and patients related to the safety concern being informed.

d. Indication of the agreement between the MA holder and the Member State's authorized authority on the provision of safety information (if necessary).
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 adapt the report to the target audience.

g. Bibliography or references to sources where you can find more detailed information about a specific safety aspect identified in the safety information sharing.

h. Reminder to report suspected adverse reactions to the Member State's authorized authority through the national spontaneous reporting system.

Safety information must not be misleading and must be presented objectively. The safety information should not contain any materials and reports that may constitute advertising and other information to promote a medicinal product.


When performing safety information sharing, it is necessary to use the full range of various media to reach target audiences and meet their growing needs. Various means of communication and channels of information transfer that should be used are discussed in detail below in subsections 11.1.5.1 to 11.1.5.5 of these Rules.

11.1.5.1. Direct Contact with Health Care Professionals.

Direct contact with health care professionals in these Rules means the submission by MA holders or the Member States' authorized authorities of important safety information directly to health care professionals to inform them about the need to take certain actions or adapt their practices concerning the medicinal product following the new safety data.
Speaking directly to health care professionals is not an answer to health care professionals' questions.

The development of information material for direct submission involves cooperation between a MA holder and the Member State's authorized authority.

The MA holder must obtain the approval of the Member State's relevant authorized authority in terms of the content of the information material for direct contact with the health care professionals and the communication plan.

The agreement between the Member State and the MA holder's authorized authority must be completed before distributing information materials by the MA holder.

Approval from the Member State's authorized authority should be obtained concerning the content of the information and the communication plan, including the target audience, the schedule for distributing information, and direct appeal to health care professionals.

The MA holder must be allocated at least 2 working days to submit comments on the Member State's authorized authority's remarks regarding the content of the information material or the communication plan.

If necessary, more time can be allocated for this procedure at the discretion of the Member State's authorized authority; the time frame can be adapted, considering the urgency of the situation.

If there are several MA holders for the same active ingredient, for which it is necessary to release information for direct appeal to health care professionals, the report should be uniform and consistent.

When preparing information for direct reference, it is recommended to involve health organizations or scientific societies, as appropriate, to ensure
that the information submitted to them is useful and adapted to the target audience.

Distribution of a direct appeal to health care professionals must be accompanied by additional tools and channels of information distribution, and the consistency of the distributed information must be ensured.

11.1.5.1.1. Direct communication with health care professionals should be included in the risk management plan as an additional measure to minimize risks.

Information for direct appeal to health care professionals should be distributed 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 authorization due to changes in a medicinal product's safety profile.

b. An important change 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 availability or discontinuation of medicinal product manufacturing may adversely affect the health care delivery system.

11.1.5.1.2. Situations in which the need for direct appeal to health care professionals should be considered:

a. The appearance in the recommendations for using a medicinal product of new important precautions or special instructions.

b. New data on the identification of previously unknown risk and changes in the frequency or severity of a known risk.

c. The emergence of reasonable evidence that the medicinal product is not as effective as previously thought.
d. New recommendations to prevent the development or control of adverse reactions or abuse or reduce the risk of medical errors.

e. Information based on the results of a continuous assessment of important potential risks, the available data on which at a certain point in time is insufficient for taking regulatory measures (in this case, direct treatment should facilitate close monitoring of the safety concern in clinical practice, reporting of adverse reactions, and informing about measures to minimize the potential risk).

The Member State's authorized authority has the right to distribute information for direct contact with health care professionals or to request a MA holder to prepare, agree and distribute information for direct contact with health care professionals if the Member State's authorized authority considers it necessary for further safe and effective use of a medicinal product.

authorized authorities of the Member States have the right to publish the final version of the information material for direct contact with health care professionals. Member State's authorized authorities may also issue additional safety reports (if necessary) and distribute information material to relevant organizations and health care professionals. This additional safety report is usually triggered when urgent action or a change in medical practice is required. It includes recommendations from the Member State's authorized authority and risk minimization measures to health care professionals. When deciding on the formation of an additional safety report by the Member States' authorized authorities, the interests of public health and the population, in general, are considered. To ensure the maximum distribution of these additional reports, the Member States' authorized authorities should select the most effective and targeted information channels. Where applicable, the outreach program may include the involvement of scientific and professional associations, patient organizations, local health authorities.
11.1.5.2. Information for Non-Specialists.

Informative material is written in a simple (non-special) language (e.g., in question and answer format) that helps patients and the public understand the scientific data and regulatory measures related to safety concerns.

Documents in layman's terms should contain recommendations and advice from the Member State's authorized authorities on how to minimize risks to patients and health care professionals concerning safety concerns. They should be accompanied by appropriate background information.

The Member States' authorized authorities post information for non-professionals on Member State medical Internet portals. They may further distribute it to relevant parties, such as patients and health care organizations, or use other means and channels of information that provide the required level of distribution and access to important safety information to the target audience.

It is recommended to involve patients and health care professionals in preparing documents in a non-professional language to ensure that the information they provide is useful and tailored to the target audience.

11.1.5.3. Information in the Press.

Press releases include press releases and press conferences that are primarily intended for journalists.

Authorized authorities of the Member States may send press releases directly to journalists in addition to posts on the websites of the Member States' authorized authorities, which will allow journalists to directly obtain information that corresponds to the scientific assessment of the Member State's authorized authority. Engaging with the media is an important way to reach a wider audience and build trust in the regulatory system.

MA holders may prepare and publish a press release presenting their position on a safety issue. Still, they must include references to all regulatory
actions taken by the Member States' authorized authority. The relevant reviews performed must be indicated in any information submitted by the MA holder.

Because press releases other than journalists can be read by other readers (e.g., health care professionals, patients, and the general public), they should reference information materials relevant to the safety concern in question. In cases where a direct appeal is also being prepared for health care professionals, they should be informed, either before publication or at the same time as the publication or distribution of the press release, to enable health care professionals to be prepared to respond to patients questions.

If 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' authorized authorities may consider holding a press conference with journalists as an effective method of informing the public.

11.1.5.4. Website.

The website is an important information-sharing tool for the public (including patients and health care professionals). Authorized authorities of the Member States, and MA holders, must ensure that important safety information posted on the websites they control is easily accessible and understandable to users. The sites' information should be constantly updated, and any outdated information should be marked accordingly or removed.

11.1.5.5. Other Means of Internet Communication.

Safety information may also be distributed on the information and telecommunications network “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.

11.1.5.6. Informational Letters and Bulletins.

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' authorized authorities can reach a large audience using web applications and other available means.

11.1.5.7. Interaction Between the authorized authorities of the Member States.

When one of the Member States' authorized authorities takes regulatory measures concerning a certain safety concern, other the Member States' authorized authorities may need to respond to inquiries or exchange information on the same issue. It is recommended to use inter-regulatory information materials in the form of documents prepared by a Member State's authorized authority to help their colleagues respond to external inquiries or exchange information on a specific safety concern.

11.1.5.8. Answers to Public Requests.

The Member States' authorized authorities and MA holders should have functioning systems for responding to inquiries from individual citizens about medicinal products. The responses should contain publicly available information and include appropriate advice for patients and health care professionals provided by the Member States' authorized authorities. Patients should be advised to consult a health care professional if questions are about advice on personalized treatment.

11.1.5.9. Other Means of Transmitting Information.

In addition to the methods of information discussed above, there are other tools and channels for transmitting safety information (e.g., publications in scientific journals and journals of professional organizations).
Some communication tools and methods can be used in risk management; risk minimization measures often include special risk information-sharing programs. The tools used in these programs, such as patient reminders, educational materials, or safety guides for health care professionals, are discussed in Section 12 of these Rules.

11.1.6. Effectiveness of Safety Information.

Safety information 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) should be used to assess the information's effectiveness. Indicators can be based on the measurement of various outcomes, including, for example, behavior, attitudes, knowledge, and other parameters or factors that characterize the effectiveness of information-sharing activities. Based on the performance assessment, conclusions should be drawn, priorities identified for further communication activities, and, if necessary, tools and practices should be adapted to meet the target audience's needs. To establish the safety information's conformity with the requirements of subparagraph 11.1.2 of these Rules, a study-based approach should be used. By applying this approach, different outcomes can be compared, including behavior, attitudes, and knowledge.

MA holders are responsible for evaluating the effectiveness of communicating safety concerns directly to health care professionals. MA holders should inform the Member States' authorized authorities about the number of health care professionals who received information in the form of direct appeal with health care professionals, the results of the assessment of the effectiveness of direct appeal, and any difficulties identified (e.g., problems with the list of recipients or deadlines and distribution
mechanisms). Appropriate corrective and preventive actions should be taken whenever there is insufficient effectiveness in direct contact with health care professionals.

11.1.7. Quality System Requirements for Safety Information.

Following the requirements for the safety information sharing quality system set out in Section 2 of these Rules, it is required that appropriate procedures are in place to ensure that safety information sharing complies with the principles defined by subparagraph 11.1.2 of these Rules. Control procedures shall be implemented and documented concerning the transmitted safety information that is the quality control object.

11.2. Interaction in the Field of Safety Information in the Territories of the Member States.

11.2.1. Interaction of the Member States' authorized authorities in the Field of Safety Information on Medicinal Products.

Within the framework of information interaction between the Member States' authorized authorities, the authorized authorities carry out a regular exchange of information concerning the safety information planned for placement.

11.2.1.1. Direct appeal to health care professionals on the safety of medicinal products authorized in the territories of the Member States

If a medicinal product is authorized in the territory of one or more Member States, the Member States' authorized authorities exchange information regarding the content of the information for direct contact with health care professionals and the information plan that has passed the approval procedure. The Member States' authorized authorities shall exchange the final version of the information material and the information transfer plan using the information interaction system.
11.2.2. Requirements for MA Holders.

A MA holder is obliged to inform the Member States' authorized authorities on the territory of which a medicinal product is authorized about his intention to make a public announcement, or inform, or post information related to pharmacovigilance information, or safety concerns, and with the use of the appropriate medicinal product. The submission of information to the Member States' authorized authorities to inform and obtain approval must be made with the condition of prohibiting its publication before the expiration of at least 24 hours before its publication. Notification of the Member States' authorized authorities simultaneously with the provision of information to the public is possible only in exceptional cases and for compelling reasons.

Such cases and reasons include a justified threat to the life, health, or well-being of the general population, as well as cases identified and justified (based on case-law) in the MA holder's Pharmacovigilance System Quality Guidelines.

The MA holder is responsible for the objectivity and accuracy of the information provided to the public.

If the MA holder receives information that a third party intends to distribute information that may affect the risk-benefit ratio of a medicinal product authorized in the territories of the Member States, the MA holder must inform the Member States' relevant authorized authorities.

11.2.3. Interaction with Third Parties.

Third parties (scientific journals, scientific societies, patient organizations, etc.) are encouraged to inform the Member States' authorized authorities about the emerging new safety information of medicinal products authorized within the Union. If it is planned to publish this information, it is
necessary to familiarize the Member States' authorized authorities with it before publication.

11.2.4. Using Language and Performing Translation when Preparing a Direct Address to Health Care Professionals.

Important safety information distributed through various information-sharing methods must be communicated to the target audience promptly and in the official language of the Member State in which the relevant medicinal product is authorized.

When forming and approving safety information intended for distribution by the Member States' authorized authorities to ensure the coordination of the content of information reports, Russian or another official language of the Member State shall be used.

Information of direct appeal to health care professionals is developed by the MA holder and submitted for approval to the Member State's authorized authority in Russian or another official language of the Member State. Distribution shall be subject to the information agreed by the Member State's authorized authority of direct appeal to health care professionals in Russian or another official language of the Member State.

12. Risk Minimization Measures

12.1. Introduction

Risk minimization 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.
The risk minimization measures included in this module should be considered in the context of the main body of the risk minimization system requirements following Section 6 of these Rules.

Risk minimization measures can include routine risk minimization measures or additional risk minimization measures. Routine risk minimization measures specified in Section 6 of these Rules apply to all medicinal products.

Routine risk minimization measures can adequately manage most safety concerns. Still, routine risk minimization measures may not be sufficient for some risks, and additional risk management measures will be needed to ensure proper risk management and (or) to improve the risk-benefit ratio of a medicinal product.

This section guides the application of additional risk minimization measures selection of risk minimization tools, and assessing the effectiveness of risk minimization measures. In certain circumstances, an assessment of effectiveness may be required for routine risk minimization measures to minimize the risk associated with safety concerns (e.g., if the SmPC 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 minimization measures also apply to routine activities.

Risk minimization measures are determined based on the safety concerns presented in the safety data sheet. Each safety concern should be considered on an individual basis; when choosing the most appropriate risk minimization measure, it is necessary to consider the severity 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.

A safety concern can be addressed in more than one risk minimization measure, and a particular risk minimization measure can extend to more than one safety concern.

The MA holder is responsible for ensuring proper control over implementing risk minimization measures included in the risk management plan approved by the Member States' authorized authorities or formulated as state approval conditions.

The Member States' authorized authorities are responsible for monitoring the introduction and implementation of risk minimization measures included in the risk management plan or formulated as conditions for state approval.

12.2. Structures and Processes

12.2.1. General Principles

Risk minimization measures aim to optimize the safe and effective use of a medicinal product throughout the 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 by targeting and (or) excluding patients or carefully monitoring treatment (specific regimen, appropriate laboratory monitoring, follow-up for patients, etc.). Risk minimization measures should guide the optimal use of the medicinal product in medical practice to ensure that the optimal product for a particular patient at the optimal dose at the right time is provided by a specialist who is properly trained in drug prescribing and patient management and with reliable information and proper control.
Most safety concerns can be properly managed with routine risk minimization measures. In certain cases, for certain important risks, routine risk minimization measures may be assessed as insufficient, and additional risk minimization measures are required for proper risk management. When determining the need for additional risk minimization activities, safety priorities regarding frequency, seriousness, severity, public health impact, and preventability should be considered. Next, an assessment is made of the possibility of achieving the set objective of minimizing risk when using routine ones. In the assumption that these measures are insufficient, it is determined which additional minimization measures are most consistent with the set objectives. Additional risk minimization measures should focus on the most important, avoidable risks, with the burden of implementing additional risk minimization measures being weighed against patients' benefit expected.

There are some different methods used as complementary risk minimization measures. This section of the regulation of drug circulation is under continuous development, and existing methods will be supplemented by new ones, including those focused on the wider use of information technologies.

The successful implementation of additional risk minimization measures requires all stakeholders' involvement, including MA holders, patients, and health care professionals. The implementation of these measures in health systems requires an assessment to ensure that the objectives of additional measures are met, as well as to determine the proportionality of the measures taken to the risk-benefit ratio of a medicinal product and the effort required on the part of health care professionals and patients to implement these measures. An important condition for introducing additional risk minimization measures, including an assessment of their effectiveness, is the
exclusion of an excessive and unreasonable burden on the health care system, MA holders, authorized authorities, and patients.

Additional risk minimization measures should 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 the set objective with key steps should guide the development of additional risk minimization measures and assess the achieved level of effectiveness.

Adequate monitoring of predetermined parameters should be ensured both during the implementation phase and effectiveness during and after implementation.

The characterization of a safety concern in the context of characterizing the risk-benefit ratio of a medicinal product, the therapeutic relevance of the product, the target population, and the necessary clinical actions to minimize risk are factors to consider when choosing risk minimization tools or methods and strategies to implement risk minimization measures to ensure the desired public health outcomes are achieved. Implementing a regular interim assessment of the effectiveness of the implemented risk minimization measures should be aimed at timely identification of their insufficient effectiveness and the implementation of appropriate corrective measures and amendments to the action plan. It is recognized that this area is an emerging field of medical science without generally accepted standards and approaches. Therefore it is important to use the appropriate elements of pharmacoepidemiology and other disciplines such as social or behavioral sciences and qualitative study methods.

The introduction of additional risk minimization measures should be seen as a program that develops specific methods and an implementation scheme and assessment strategy. The risk minimization plan is an integral
part of the risk management plan. The risk minimization plan should include the following sections:

a. Rationale: If it is necessary to introduce additional risk minimization measures, this section should justify the proposed additional risk minimization measures.

b. Objectives: This section should identify specific objectives for each of the proposed complementary measures and provide a clear description of how the proposed complementary risk minimization measure will address a specific safety concern.

c. Description: This section should describe the additional risk minimization measures selected, including a description of the tools or techniques that will be used and the key content elements.

d. Implementation Plan: This section should provide a detailed description of proposals for the implementation of additional risk minimization 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 these measures with other MA holders, if necessary).

e. Evaluation Plan: This section should provide a detailed plan with key steps for evaluating the effectiveness of additional risk minimization measures in terms of performing the planned process and overall indicators of impact on outcomes (e.g., risk reduction).

12.2.2. Risk Minimization Measures.

Additional risk minimization 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 minimization measures should be scientifically based, developed, and presented by appropriately qualified specialists.
Additional risk minimization measures can vary in purpose, design, target audience, and complexity. These measures may be used to ensure the proper selection procedure for appropriate 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.

Additionally, specific risk minimization measures can be developed concerning the risk of medical 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.

If a request for additional risk minimization measures is made, the rationale for the request should be documented, and specific safety concerns should be identified, and detailed planning and risk assessment steps should be provided.

Additional risk minimization measures may include the following:

a. Educational program.
b. Controlled access program.
c. Other risk minimization measures.

12.2.2.1. Educational Program.

Additional risk minimization tools or methods used in an educational program are based on targeted communication with the presentation of information in the summary of product characteristics or package insert. Any educational material should be oriented towards achieving specific objectives of risk minimization.

The objective of the educational program is to optimize the use of a medicinal product by positively influencing the actions of health care
professionals and patients to minimize risk. Educational materials should be created to assume that there is a feasible and effective recommendation for targeted education and that the application of this measure is considered important and significant for minimizing risk and (or) optimizing the risk-benefit ratio.

Educational tools used in the context of an educational program can have several different target audiences, can address more than one safety concern, and can be communicated using a combination of tools and media (in hard copy, audio, video, in the information and telecommunications network “Internet,” personal training). It is recommended to present materials in a range of formats to ensure access, including in the event of failure of the means of informing or inability to use the information and telecommunications network “Internet.” If possible, the level of adaptation of the tool used and the media for the target audience (e.g., the suitability of the language used, images, diagrams, or other graphic support of information) should be tested on the target population in advance to optimize the results of the additional activities phase in the form of educational programs.

The content of any educational material should be fully consistent with currently approved drug information, such as the summary of product characteristics or package insert. It should complement rather than duplicate information in the SmPC or PI. Advertising elements (direct or veiled, for example, logo, distinctive color design of a product, stimulating images) should not be included in the content, and the emphasis of educational materials should be on the risks related to a medicinal product and the management of such risks, requiring additional risk minimization measures.

Any educational program should be completely separated from advertising activities, and the contact information of doctors and patients
obtained through educational programs should not be used for advertising purposes.

The educational tools described below can be considered individually or in combination when designing an educational program of additional risk minimization.

12.2.2.1.1. Educational Tools.

Educational tools should have a specific focus and include an unambiguous definition of risk for the significant risks considered and the specific actions taken by health care professionals and (or) patients to minimize such risks.

This information should focus on clearly defined actions relevant to specific safety concerns in terms of minimizing risk and should not include information that is not directly related to the safety concern and appropriately presented in the summary of product characteristics or package insert. Educational materials should include a link to the summary of product characteristics or package insert.

In addition to an introduction indicating the need for educational materials to ensure safety, effectiveness of use, and proper management of important risks, items of information for inclusion in educational tools or techniques may include:

a. Guidelines for prescribing a medication, including patient selection, monitoring, and control, aimed at minimizing important selective risks.

b. Guidelines for managing such risks (for health care professionals, patients, or caregivers).

c. Guidelines for reporting identified adverse reactions of particular interest to characterize a particular risk.

12.2.2.1.1.1. Educational tools or techniques for health care professionals.
The purpose of any educational tool or method for health care professionals is to provide specific recommendations for use, and (or) contraindications, and (or) precautions related to the medicinal product and specific risks that need additional risk minimization 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.

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, focusing on early detection and management of adverse reactions. At the same time, posters may contain applicable therapeutic guidelines or drug regimens. Preference may be given to other formats, depending on the focus, volume of information, target audience, and other factors.

12.2.2.1.1.2. Educational tools or techniques for patients and their caregivers.

Patient education tools or techniques should aim to improve patient or caregiver understanding of signs and symptoms essential for the early detection of certain adverse reactions that require additional risk minimization measures and optimize patient management. If appropriate, an educational tool or method can be used to provide information and remind the patient of important actions (such as keeping records of drug dosing or diagnostic procedures to be recorded or performed by the patient, followed
by a discussion with health care professionals to ensure compliance with any steps necessary for the effective use of a medicinal product, etc.).

12.2.2.1.1.3. Memo to Patients.

The purpose of this tool is to ensure that specific information regarding a patient's current treatment and treatment-related risks (such as potential interactions with other medicinal products) is always available to the patient and available to the appropriate health care professional. The information should contain the minimum necessary to transfer key instructions to minimize risk and necessary actions to alleviate the condition under all circumstances, including emergencies. Portability should be one of the key characteristics of this tool.

12.2.2.1.2. Controlled access program.

A controlled access program consists of operational measures aimed at controlling access to a medicinal product beyond the level of control guaranteed by routine risk minimization measures, i.e., the regulatory status of the product. Controlled access should be considered as a method of minimizing the serious risk (e.g., the risk of developing life-threatening adverse events) for a drug with proven benefit (e.g., drugs for the treatment of life-threatening diseases for which there is no alternative treatment for the target population or a subgroup of the target population due to the ineffectiveness of alternative treatment), which cannot be achieved without additional minimization measures due to the risk of exposure to patients' health.

Examples of requirements that must be met before prescribing a drug and (or) dispensing and (or) using it in a controlled-access program are listed below (they can be performed individually or in combination with other requirements):
a. Specific methods of control and (or) examination of the patient to ensure compliance with certain clinical criteria.

b. The doctor who prescribes the drug, the pharmaceutical worker who dispenses the drug, and (or) the patient document their receipt and understanding of information regarding the serious risk associated with the drug use.

c. Precise procedures for the patient's systematic follow-up through registration in a special data collection system (in the patient register), etc.

d. Medicinal products can only be obtained from pharmacies licensed to dispense such a product.

In certain cases, requirements for special examination or monitoring of the patient's condition may be used as a controlled-access tool. For example, monitoring the patient's condition, laboratory parameters, or other characteristics (ECG, etc.) before treatment and (or) during treatment, liver function tests, regular blood tests, a pregnancy test (which can be a component of a pregnancy prevention program). Measures should be put in place to ensure control following the summary of product characteristics when this is a critical factor in terms of the risk-benefit ratio of the medicinal product.

12.2.2.1.3. Other Risk Minimization Measures.

12.2.2.1.3.1. Controlled Distribution System

A controlled distribution system refers to the types of measures designed to ensure that all stages of the drug distribution chain are tracked to the prescribing and/or dispensing of a drug by pharmacies. Orders and shipments of a medicinal product by one or more identified distributors facilitate the traceability of the product. For example, these measures could be considered for those medicinal products controlled in each country by relevant national legislation to prevent drug misuse and abuse.
12.2.2.1.3.2. Pregnancy Prevention Program.

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 should ensure the implementation of such a monitoring mechanism in which female patients were not pregnant at the beginning of therapy or did not become pregnant during the course of treatment and (or) a certain period of time after the cessation of therapy. A pregnancy prevention program can also target male patients if the biological father's use of the drug could have negative consequences for the pregnancy outcome.

A pregnancy prevention program combines educational tools and appropriate tools to control access to the medicinal product. The following elements should be considered both individually and collectively when planning a pregnancy prevention program:

a. Educational tools aimed at health care 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 different 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 level 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 unintended pregnancy and assessing the outcome of an accidental pregnancy.
Consideration should also be given to the feasibility and design of 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). The use of the tool for systematic collection of information on pregnancy cases and outcomes contributes to collecting information on the effectiveness of the implemented pregnancy prevention program and data on risk characterization, especially at the initial post-marketing stage with a significant limitation or lack of data on pregnancy outcomes in humans.

12.2.2.1.3.2. Direct Appeal to Health Care Professionals.

Direct contact with health care professionals is an active form of safety communication, through which important information is presented by the MA holder or the Member States' authorized authority directly to health care personnel to inform them of the need to take serious action or adapt accepted medical practice to minimize certain risks and (or) reducing the severity of adverse drug reactions specified in Section 11 of these Rules.

12.2.3. Implementation of Risk Minimization Measures.

Additional risk minimization measures may include one or more active measures to be implemented and implemented within a specific target group. Adequate attention should be paid to both the timing and frequency of implementation of risk minimization measures and procedures to achieve the objectives in the target group. For example, one-time educational tool execution may not be sufficient to ensure that information is reached for all potential prescribers and (or) consumers, including new health care providers and consumers. There may be a need for additional periodic distribution of educational tools or program methods to implement risk minimization measures. Due regard should be paid to the general format of educational tools or methods to ensure clear distinction with different promotional
materials. Since risk minimization measures are aimed at different purposes, some of these measures, such as reminders, controlled access programs, and pregnancy prevention programs, should, in most cases, be applied downstream of the drug. In contrast, others, such as direct information sharing with health care professionals and educational materials, may not be required in subsequent drug administration stages. The validity of each risk minimization measure and the need for 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's approval. The submission of educational materials for approval to the Member State's authorized authority should be carried out separately from the transfer of advertising material. At the same time, the cover letter should 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 should ensure that the distribution systems in place are adequate for the intended purpose of the risk minimization measure are controlled and audited.

12.2.4. Evaluation of the Effectiveness of Risk Minimization Measures.

Evaluating the effectiveness of risk minimization measures is necessary to establish the effectiveness of active risk minimization measures, the causes of inefficiency, and the need for corrective action. Evaluation of the effectiveness of measures is carried out for each measure of risk minimization and the risk minimization program as a whole.

The timing of each aspect of an active measure should be carefully planned as part of the risk management plan before initiating measures, taking into account the time required to initiate risk minimization measures,
the amount of drug use by the health care system, and other factors that affect
the timing of planned activities.

A periodic review of the effectiveness of one or more specific
instruments or the program as a whole should be planned. The following
reference points in time apply, which are of particular importance for the
evaluation of program performance:

After the initial start of implementing the risk minimization program
(e.g., within 12 – 18 months) to ensure the possibility of making changes if
their need is determined.

At the stage of evaluating the registration approval.

Assessing the effectiveness of risk minimization measures at all
implementation stages also includes determining the need to continue
applying the assessed additional risk minimization measure.

Evaluation of the effectiveness of measures should consider various
aspects of the implemented risk minimization measure: the process itself (that
is, the degree of implementation of the planned program), its impact on
awareness and changes in the behavior of the target group, and the result (to
what extent the risk minimization objectives were achieved and in a short or
long term). The design of the assessment strategy identifies aspects of the
process and results that can be correctly measured to avoid inaccurate or
misleading data or unduly burdening the health care system or other parties
involved in the risk minimization measures being implemented. The timing
of evaluating each aspect of the proactive measure being undertaken, and
establishing the correct metrics against which to assess the effectiveness of
the risk minimization tool, should be carefully considered and planned before
initiating risk minimization measures.

To assess the effectiveness of risk minimization measures, 2 groups of
indicators should be used:
a. Process indicators.

b. Results indicators.

Process indicators are needed to collect evidence of the success of all stages of risk minimization measures. This group of process indicators should assess the degree of implementation of the planned program and the achievement of the required impact on the behavior or actions of the target group. Program performance indicators should 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 minimization measures have or have not achieved the desired control of specific risks.

Outcome indicators provide an overall assessment of the degree of risk control achieved by implementing risk minimization measures. For example, if the aim of an intervention is to reduce the frequency and (or) severity of adverse reactions, the ultimate success criterion will be tied to that objective.

In the rare cases where performance measurement is reasonably impracticable (e.g., an unreasonably large number of patients at risk, very rare adverse events), the assessment of effectiveness can be based on a reliable interpretation of the process indicators.

Based on the procedure results for assessing the effectiveness of risk minimization measures, a conclusion is made about the possibility of further implementation of the assessed risk minimization measure without changes or the need to change it. Evaluation of the effectiveness of risk minimization measures may indicate that risk minimization activities are insufficient and should 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 minimization 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 minimization, or the frequency of implementation of certain measures for risk minimization, 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 minimization).

In addition to assessing the effectiveness of risk minimization measures in managing safety concerns, it is also important to assess whether an additional risk minimization 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 health care system, stopping the use of a medicinal product by patients, including in cases of a positive risk-benefit ratio for these patients.

Studies assessing the effectiveness of risk management measures are post-authorization safety studies. Thus, when conducting a study to assess behavior or safety indicators, the requirements for post-authorization safety studies defined in Section 8 of these Rules must be met. This guidance does not apply to the measurement of simple process indicators (e.g., distribution of risk minimization tools to the target population). Where appropriate, methodological standards for evaluating studies in pharmacoepidemiology may be used.

12.2.4.1. Process Indicators.

Process indicators are parameters for assessing the volume of implementation of the original program and (or) changes in its
implementation. Process indicators should complement, not replace, the assessment of achievement of intended objectives by implementing risk minimization measures (outcome indicators). Depending on the nature of the active measures, various process indicators can be defined to assess their effectiveness.

12.2.4.1.1. Reaching the Target Population.

When risk minimization measures include providing information and guidance to health care professionals and (or) patients through educational methods, distribution assessment measures should be used to obtain baseline performance data. These indicators should focus on assessing the delivery of the tool used to the target group and assessing the actual receipt of the materials by the target group.

12.2.4.1.2. Clinical Knowledge Assessment.

To assess the target group's awareness and the level of knowledge gained through educational, operational measures and (or) using other methods of information delivery, rigorous scientific survey methods should be applied.

The survey usually includes basic standard questions, the answers to which can be provided by telephone, in a personal interview, or sent by email. The survey should be repeated periodically.

This approach can be tailored to monitor attitudes and awareness in representative groups of each target audience of health care professionals and (or) patients and performed using appropriate psychometric values. Adequate sample size should be determined for the assessment to be included using randomization. The use of advocacy groups or patient support groups for the knowledge-based survey may be considered biased in nature due to self-selection and should be avoided.
Due consideration should be given to the objectives of the survey, study design, sample size and representativeness, operational definitions of dependent and independent variables, and statistical analysis. Careful attention should also be paid to selecting the most appropriate data collection tools (questionnaires, questionnaires, etc.).

12.2.4.1.3. Clinical Action Evaluation.

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).

Studies on using a medicinal product through the recycling of electronic health records should be considered a valuable tool for quantifying clinical performance if the target group and database are adequately represented.

Analysis of prescription sheets, especially concerning other patient 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.

Applying appropriate 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 minimization goes beyond just describing the evidence. Particular attention should be paid to the conduct and interpretation of the results of studies assessing the use of medicinal products in countries, including the authorization 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 national prescribing guidelines, health system
aspects, local medical practice and limits on treatment reimbursement. This
diversity of national health care delivery systems within and outside the
Member States may warrant study with the same objectives in several
countries.

Behavioral studies based on data collected through analytic surveys
should only be considered when preexisting data were not available to
evaluate clinical actions.

12.2.4.2. Results indicators.

The ultimate indicators of the success of the risk minimization program
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). The safety results should be indicators of the success of the risk
minimization program.

An assessment based on these indicators should 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-authorization safety studies. Consideration should be given to
using appropriate safety outcomes (e.g., a surrogate endpoint, such as an
appropriate biomarker, as a substitute for the clinical endpoint) if such an
approach facilitates the performance evaluation of the risk minimization
measures being implemented.

Under any approach, the scientific and recognized epidemiological
study principles should always guide the evaluation of the outcome indicator
in question.

Consideration should be given to the comparison of frequency before
and after the implementation of risk minimization measures.

When it is not feasible to perform a pre- and post-intervention
assessment and calculation (e.g., risk minimization measures were put in
place at the time of marketing authorization), the outcome rate obtained at the post-intervention stage is correlated with a predetermined reference value obtained from the literature, 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 must be properly justified.

Methods for assessing the effectiveness of risk minimization measures should be comparable with the risks being minimized. The use of the indicator (the number of reports of suspected adverse reactions in a fixed period of time) may be acceptable in evaluating the effectiveness of routine risk minimization measures. Spontaneous reporting as an indicator should be considered with caution when assessing the incidence of adverse reactions in the target population except in special circumstances when, for example, 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.

In such circumstances, where a direct determination of the degree of risk in the group in question is impracticable, spontaneous reports might allow an estimate to be made of the approximate frequency of adverse reactions in the group, provided that some reasonable data can be obtained to estimate the rate of repetition in the context of drug use.

The inherent uncertainties that affect the level of reporting of suspected adverse reactions can lead to misleading results. For example, introducing a risk minimization program in response to a safety concern identified during the post-authorization monitoring phase of a medicinal product can raise awareness of certain adverse reactions, which may ultimately lead to an increased reporting rate.
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.

12.2.5. Coordination.

If several medicinal products, including medicinal products with the same active ingredient, are available on the market, a holistic approach should be developed to apply additional risk minimization measures provided by the authorized authorities of the Member States. When there is a need for coordination actions for a group of drugs, a coordinated approach must be developed. In such circumstances, planning should ensure that the effectiveness of risk minimization measures is evaluated for each medicinal product and products in combination.


Although many experts may be involved in the development and implementation of risk minimization measures, the ultimate responsibility for the quality, accuracy, and scientific integrity of such measures rests with the MA holder and the MA holder's pharmacovigilance officer.

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 minimization measures with the approved summary of product characteristics and the package inserts, and must also apply the quality principles specified in Section 2 of these Rules. Traceable versions of the risk management plan should be submitted for review and assessment by the Member States' authorized authorities. The reports, the risk management plan, and the risk management systems included in the plan and any documents regarding risk minimization measures may be audited or inspected.
The MA holder shall ensure that mechanisms for reporting the results of studies or analyzes to assess the effectiveness of risk minimization measures are documented. These documents can be audited or inspected.

12.3. Responsibility of the authorized authorities of the Member States

Authorized authorities of the Member States are responsible at the national level to implement additional risk minimization measures applied as a condition for the safe and effective use of a medicinal product. Additional risk minimization measures established for medicinal products during registration under a decentralized procedure or recognition procedure and additional risk minimization measures are included in the risk management plan and are authorization conditions. The introduction of additional risk minimization measures at the national 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 health systems, and feasibility at the national level.

Concerning risk minimization measures that were introduced after getting the marketing authorization, the Member States’ authorized authorities must ensure that the submitted measures are promptly reviewed and agreed with the MA holder.

authorized authorities of the Member States, if necessary, can assist in the harmonization of the implemented risk minimization measures for generic medicinal products (generics) with the same active ingredient. If it is necessary to introduce additional risk minimization measures for generic medicinal products (generics) due to problems related to the safety of the active substance, the risk minimization measures applied to the generic
products (generics) should be brought in line with the risk minimization measures for the reference product. Under certain circumstances, additional risk minimization measures may be required for hybrid medicinal products and the risk minimization measures introduced for the reference product (e.g., due to differences in formulation, route of administration, or incompatibility problems). An authorized authority of a Member State can help identify the key elements of risk minimization tools to be implemented by MA holders and provide access to these recommendations by posting on a web portal to ensure harmonized implementation of risk minimization measures at the national level.

Authorized authorities of the Member States should ensure that any tool or method is used to minimize the risk. Authorized 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.

The Member State's authorized authority makes an independent decision regarding selecting appropriate national educational materials and other tools or methods to minimize risk; at the same time, it is recommended that authorized authorities of the Member States coordinate the key elements of the risk management plan. Additional risk minimization measures may need to be evaluated in the territory of a Member State because of the local circumstances of health care delivery or if, due to national circumstances, the results of effectiveness evaluation studies performed in other States cannot be extrapolated to the results of the risk minimization measures program performed in the territory of the Member State concerned.
authorities of member states at the national level monitor the results of the introduction of risk minimization measures.

If a patient memo is included in the outer packaging, this patient memo is considered part of the labeling of the medicinal product. It is subject to approval by the authorized authority of the Member State.

12.4. Responsibility of MA Holders

MA holders are responsible for compliance with the conditions for approval of medicinal products, including compliance with all conditions or restrictions regarding the safe use of the product in a certain territory.

The registrant must define the objectives of the proposed additional risk minimization measures and the indicators for assessing their effectiveness. The MA holder is encouraged to coordinate the risk minimization plans with the Member States' authorized authorities as early as possible in cases where it is likely that certain components of the risk minimization measures will need to be adapted to the different health system conditions in the different Member States. Any additional operational risk minimization measures shall be designed following the general principles specified in Sections 12.2.1 and 12.2.2 of this Regulation and shall be fully documented in a risk minimization program in accordance with Section 6 of these Rules.

Measures approved by the authorized authority of a Member State in terms of minimizing the risk must be implemented at the Member State level. The MA holder must provide information regarding the status of implementation of additional risk minimization measures based on the results of a preliminary agreement with the authorized authorities of the Member States, and inform the authorized authorities of the Member States regarding any changes, difficulties, or issues arising from the implementation of additional risk minimization measures. Any relevant changes concerning
tools or methods for implementing risk minimization measures must be agreed upon with the Member States' authorized authorities.

When introducing information technology-based tools or methods, MA holders shall apply the requirements specific to each Member State, considering potential problems of accessibility, recognizability, liability, confidentiality, and data protection.

For generic products (generics), the MA holder must develop risk minimization 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 must be properly coordinated to minimize the burden on health systems.

Evaluation of the effectiveness of risk minimization measures concerning generic products (generics) is carried out by the MA holder in cooperation with the Member States' authorized authorities. Where a study is warranted, a collaborative study is strongly recommended to minimize the burden on health systems. For example, if a prospective cohort study is scheduled, study enrollment should 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 any new risk inherent in a particular product.

The MA holder should monitor the results of the risk minimization measures that are included in the risk management plan. The general principles for assessing effectiveness are specified in paragraph 12.2.4 of these Rules.

The MA holder must submit a report on the assessment of the effectiveness of additional risk minimization measures related to the assessment of the risk-benefit ratio in the periodic safety update report.
The MA holder must ensure timely communication with the Member States' authorized authorities to carry out the appropriate regulatory assessment and actions in accordance with Section 5 of these Rules.

12.5. Health Care Professionals and Patients

Health care professionals and patients are not legally responsible for fulfilling their pharmacovigilance obligations. Simultaneously, the interaction of health care 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 minimization measures that may be introduced to ensure the safe and effective use of medicinal products.

12.6. Impact of the effectiveness of risk minimization measures on a risk management plan and periodic safety update report

Updates to the periodic safety update report and risk management plan should include a summary assessment of the impact of additional risk minimization measures introduced to reduce important risks associated with medicinal product use. In the risk management plan, the emphasis should be on how the activities performed and their results are reflected in the planning of risk minimization and (or) pharmacovigilance activities. 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 should be made. Emphasis should be placed on information obtained during the reporting period or since the implementation of recent risk minimization measures.

The results of assessing the effectiveness of risk minimization measures 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 minimization measures. This critique may include a reference to experience outside of the Member States (if any).

Evaluation of the effectiveness of risk minimization measures should focus on whether they have successfully minimized the target risk. Evaluation is performed using a combination of process and result indicators according to paragraph 12.2.4 of these Rules. It is recommended that a distinction be made between the risk minimization measures introduced at the time of issuance of the marketing authorization and those that were introduced later at the post-authorization stage.

An assessment of the effectiveness of risk minimization measures should be presented considering the following recommendations:

a) Assessment should provide context by:

Summary of the introduced risk minimization measures.
Defining their objectives.
Descriptions of the selected process and indicators of the result.

b) Assessment should include appropriate analysis of the nature of the adverse reactions, including their severity and preventability. Where appropriate, logistical factors that may affect the clinical performance of risk minimization measures should also be included.

c) The assessment should include examining the implementation of risk minimization 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 should be the key endpoints in assessing the degree of achievement of the assigned objectives in implementing risk minimization measures.
Proposals for changes to improve risk management measures should be presented in the appropriate section of the periodic safety update report. The risk minimization plan should be updated based on information received regarding the risk minimization measures' effectiveness.

The frequency of updating the risk management plan should be proportional to the risks associated with medicinal product use. Updates to the risk management plan should focus on the risk minimization program and provide updates on the implementation of risk minimization measures, where applicable.

If a limited number of sections are updated, they must be listed in the cover letter when submitting the documentation. If based on the results of the implementation of risk minimization measures, changes are required in the summary of product characteristics. The procedure for making changes to the information on a medicinal product should be performed. Based on the preparation of the periodic safety update report, the need to update the information on the medicinal product can also be determined.

12.7. Transparency

Authorized authorities of the Member States ensure the transparency and availability of information on the introduced risk minimization measures by posting the following information on the relevant Internet portals: the current version of the summary of product characteristics, a summary of the risk management plan indicating the risk minimization measures introduced.

On the national Internet portal of medicinal products of the Member States, authorized authorities of the Member States shall provide public access to the following information:

Summary of product characteristics and package insert.
The established conditions of the marketing authorization, including the terms for fulfilling the conditions.

Summary of the risk management plan, including the pharmacovigilance plan and risk minimization measures.

Details of additional risk minimization measures required as a condition of marketing authorization (e.g., if risk information-sharing tools consist of printed material, a copy is provided, or if possible, electronic access to educational material, patient memo, checklists, or other risk information-sharing tools).

13. Additional Monitoring

13.1. Introduction

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.

Authorization 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.

However, not all risks can be identified by the initial approval time; some risks are identified at the post-authorization stage with the widespread use of a medicinal product throughout the entire life cycle of the product.

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 authorization, which means the introduction of the concept of additional monitoring for some products.
Authorized authorities of the Member States create, keep up to date, and publish 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 ask health care professionals to report any suspected adverse reactions.”

13.2. Structures and Processes

13.2.1. Principles for Assigning Additional Monitoring Status to a Medicinal Product.

Registration of all medicinal products is carried out based on recognizing the risk-benefit ratio as positive, considering the information available at the time of approval (data from clinical studies 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 using a medicinal product may have been assessed in different settings from everyday medical practice; for example, clinical studies 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 authorized authorities of the Member States carry out constant monitoring of 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 state registration to identify significant new safety concerns as quickly as possible and take immediate action. To improve the effectiveness of monitoring the safety of certain medicinal products and to stimulate the submission of spontaneous reports of identified adverse reactions, the concept of additional monitoring has been introduced.

The status of additional monitoring can be assigned to a medicinal product while getting the marketing authorization or at later stages of the life cycle of a medicinal product if a new safety concern is identified in the process of post-authorization monitoring. In particular, the status of additional monitoring is important when issuing marketing authorizations for medicinal products containing a new active ingredient for all biological medicinal products, which are priorities for pharmacovigilance. Authorized authorities of the Member States may also require the introduction of additional monitoring status for a medicinal product under certain circumstances, such as the post-authorization safety study results or restrictions on the safe and effective use of the product.

13.2.2. Data Exchange and Transparency.

The status of additional monitoring should be communicated to health care 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 authorized authority should constantly update the publicly available list of medicinal products with additional monitoring in terms of the circulation of medicines. Besides, health care professionals and patients should be able to recognize these products by their labeling easily. Publication of the list, together with the
associated report, should encourage health care professionals and patients to report any suspected adverse drug reactions that need to be further monitored.

13.3. Criteria for the Inclusion of a Medicinal Product to the Additional Monitoring List

13.3.1. Mandatory Inclusion Criteria.

The list of medicinal products subject to additional monitoring includes the following categories of medicinal products:

a. Medicinal products authorized in the Member States territories containing a new active substance that, before the entry into force of these Rules, were not authorized in any Member States as part of any medicinal product.

b. Biological medicinal products authorized a Member State territory after the entry into force of these Rules.

c. Medicinal products for which the Member State's authorized authority requested a post-authorization safety study at the time of issuance of the marketing authorization or after issuance of the marketing authorization.

13.3.2. Additional (Optional) Inclusion Criteria.

At the request of the authorized authority of the Member State, medicinal products can be included in the list of 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 authorized 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 authorized authority has established an obligation for the MA holder to conduct a post-authorization study of effectiveness.

The decision to include a medicinal product in the additional monitoring list should also consider the expediency of this status, considering other additional pharmacovigilance activities proposed in the risk management plan.

13.4. Criteria for Determining the Initial Adjustment Time for the List of Medicinal Products Subject to Additional Monitoring

13.4.1. Mandatory Criteria.

For medicinal products containing new active substances and all biological products, the initial period of inclusion is 5 years from the date of authorization in the Member State territory.

13.4.2. Additional Criteria.

For medicinal products included in the list based on the establishment of certain conditions (post-registration studies of safety, efficacy, risk management system requirements), the period of inclusion in the list is related to fulfilling relevant conditions and obligations imposed on the MA holder. The Member States' authorized authority determines it according to their fulfillment and the results obtained.

During the life cycle of a medicinal product, it may be repeatedly included in the list of medicinal products subject to additional monitoring.

13.5. Obligations of authorized authorities of the Member States

Authorized authorities of the Member States should provide the following:
a. Information sharing with authorized authorities of other Member States about the decision taken to include authorized (approved) medicinal products in the list of subject to additional monitoring, provide an electronic link to the web page of the Member State's authorized authority, where public access to information on the medicinal product and a summary of the risk management plan is open.

b. Publishing a list of medicinal products authorized in the Member States territories, which are subject to additional monitoring on websites in the information and telecommunications network “Internet.” The list contains an electronic link to the website of the authorized authority of the Member State in the information and telecommunications network “Internet,” where public access to information on the medicinal product and a summary of the risk management plan is open.

c. Information sharing with authorized authorities of other Member States about medicinal products authorized under the national procedure included in the list of products subject to additional monitoring.

d. Considering the list of medicinal products subject to additional monitoring when determining the frequency and characteristics of the signal detection procedures.

e. Information sharing with a relevant MA holder about the decision to be included in the list of medicinal products for additional monitoring.

f. Taking all appropriate measures to ensure that health care professionals and patients report any suspected adverse reactions to a medicinal product on the list of products for additional monitoring.

g. Carrying out a monthly update of the list of medicinal products for additional monitoring.
13.6. Obligations of MA Holders

MA holder must provide the following.

a. Including the summary of product characteristics and the package inserts included in the list of subject to additional monitoring, the black triangle symbol ▼, and a standard explanation of additional monitoring.

b. Including information on the status of additional monitoring in any material that will be distributed to health care professionals and patients and should make every effort to stimulate the reporting of adverse reactions, as agreed with the Member States' authorized authorities.

c. Providing the authorized authorities of the Member States with data and confirmations of the status of fulfilling any conditions imposed by these authorized authorities.

d. Submitting appropriate changes to the summary of product characteristics and package insert for the inclusion or removal of the black symbol and standardized explanatory wording in the manner prescribed by the Rules for the approval and examination of medicinal products for human use 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.

13.7. Black Symbol and Explanatory Note

For drugs on the list of drugs 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.”

After a medicinal product is included in or removed from the list, the MA holder is obliged to make the appropriate changes in the summary of product characteristics and package insert to include or remove the black symbol (as appropriate), a statement, and a standard explanatory note.

If the decision to include a medicinal product in the list or remove it from the list is made when performing a procedure established by the right of the Union or the legislation of a Member State (approval or renewal procedures, changes in the summary of product characteristics, etc.), then the content of the summary of product characteristics and package insert need to be updated before the completion of the procedure to include or remove the black triangle and standard explanatory note in the drug information sheet.

If the decision on the inclusion of a medicinal product in the list or removal from it is made outside the framework of the procedure established by international treaties and acts constituting the right of the Union, or the legislation of the Member States, the MA holder is obliged, following the established procedure, to make appropriate changes to the summary of product characteristics and package insert.”