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A REGULATION

By Turkish Medicines and Medical Devices Agency

REGULATION ON THE SAFETY OF MEDICINAL PRODUCTS

CHAPTER ONE
Purpose, Scope, Basis and Definitions

Purpose

ARTICLE 1 – (Amended:OG-21/7/2022-31899)

(1) The purpose of this Regulation is to determine the procedures and principles regarding the systematic monitoring of adverse reactions and benefit/risk balances, collecting, recording, evaluating, archiving information on this subject, establishing contact between the parties and taking the necessary measures to minimize the harm caused by medicines in order to ensure the safe use of medicines and to contribute to the protection of public health.

Scope

ARTICLE 2 – (1) This Regulation applies to monitoring, research, recording, archiving and assessment activities, and natural or juristic persons undertaking such activities, for securing the safety of authorized or unauthorized medicinal products in Turkey.

Basis

ARTICLE 3 – (1) This Regulation; has been prepared on the basis of:

a) **(Amended:OG-21/7/2022-31899)** the provisions of the Law on Pharmaceutical and Medical Preparations dated 14/5/1928 and numbered 1262, paragraph (k) of the first paragraph of Article 3 of the Health Services Basic Law No. 3359 dated 7/5/1987 and Articles 508 and 796 of the Presidential Decree on the Organization of Ministries and Institutions and Organizations and Other Institutions and Organizations Related, Affiliated to Ministries dated 15/07/2018 and numbered 4.

b) Directive 2010/84/EC governing medicinal products in the European Union.

Definitions

ARTICLE 4 – (1) For the purposes of this Regulation, the following terms will have the following meanings:

a) Adverse reaction / suspected adverse reaction: A response to a medicinal product which is noxious and unintended.

b) Ministry: Ministry of Health.

c) Unexpected adverse reaction: An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

ç) Individual case safety report: An adverse drug reaction report.

d) Serious adverse reaction: An adverse reaction which results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

e) Pharmacovigilance: Science and activities relation to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

f) **(Amended:OG-21/7/2022-31899)** Pharmacovigilance provincial responsible person: the relevant head or deputy head of department of the provincial health directorate responsible for the coordination, training and control of the pharmacovigilance contact points in the province where they work.

g) Pharmacovigilance contact point: A medical doctor, pharmacist, or, where these are not available, dental practitioner responsible for promoting reporting of adverse reactions and undertaking training and educational activities at the healthcare institution where they work, and forward any adverse reaction reports received to TÜFAM.

ğ) Pharmacovigilance system: A system used by marketing authorization holders and applicants to fulfill the tasks and responsibilities listed in this Regulation and designed to monitor the safety of medicinal products and detect any potential changes to their risk-benefit balance.

h) Pharmacovigilance system master file: A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more medicinal products.

ı) Qualified person responsible for pharmacovigilance: A physician or pharmacist employed by a marketing authorization holder or a contact pharmacovigilance service provider at a national level to fulfill the requirements of this Regulation.

i) **(Amended:OG-21/7/2022-31899)** Medicine (Medicinal product for human use): Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

j) Abuse of medicinal products: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

k) Agency: Turkish Medicines and Medical Devices Agency.

l) MedDRA: A medical dictionary created by the International Conference on Harmonization for use in connection with regulatory activities.

m) Periodic risk-benefit assessment report: A post-authorization report issued by the marketing authorization holder in a specific format in predefined time intervals, providing an assessment of the medicinal product's risk-benefit balance.

n) Risk: Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health, including any risks of undesirable effects on the environment.

o) Risk management plan: A detailed description of the risk management system.

ö) Risk management system: A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relation to a medicinal product, including the assessment of the effectiveness of those activities and interventions.

p) Post-authorization safety study: Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

r) Healthcare professional: For the purpose of reporting suspected adverse reactions, a physician, pharmacist, dental practitioner, nurse or midwife.

s) Signal: Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

ş) Contract pharmacovigilance service provider: An organization subject to Agency approval and oversight, meeting the requirements specified in the applicable guideline, employing at least one qualified person responsible for pharmacovigilance and another person to deputize for the former, appointed by the marketing authorization holder with all or some of the pharmacovigilance obligations of the marketing authorization holder as set forth in a written document.

t) Spontaneous report: An unsolicited communication by a healthcare professional or consumer to the Agency or the marketing authorization holder, that describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme

u) TÜFAM: Turkish Pharmacovigilance Center, established within Turkish Medicines and Medical Devices Agency.

ü) TÜFAM reporting form: A form used to report one or more suspected adverse reactions that occur in a single patient to a specific medicinal product at a specific point in time.

v) Consumer: For the purpose of reporting suspected adverse reactions, a person who is not a a healthcare professional such as a patient or lawyer, friend or relative/parent/child of a patient.

y) Risk-benefit balance: An evaluation of the therapeutic effects of the medicinal product in relation to any risks relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health.

CHAPTER TWO
Obligations of the parties

Responsibilities of the marketing authorization holder

ARTICLE 5 – The marketing authorization holder will:

(1) assure the safety of its medicinal products. For this purpose, the marketing authorization holder is responsible to continuously monitor the safety of its medicinal products, notify the Agency of any changes that may have an effect on the risk-balance assessment of the medicinal product, including any restrictions or prohibitions introduced by competent authorizations of other countries where the product is authorized, and maintain product information up-to-date in the light of current scientific data. This responsibility includes any data, whether positive or negative, for any population or indications,

independent from whether the medicinal product is authorized for such use.

(2) establish a pharmacovigilance system to undertake pharmacovigilance, and take appropriate measures to minimize or eliminate risks based on the assessment of information obtained through such system.

(3) use MedDRA terminology for the classification of adverse reactions occurring in relation to its medicinal products.

(4) conduct regular audits of its pharmacovigilance system, noting the audit findings in the pharmacovigilance system master file. The marketing authorization holder will cause the preparation and implementation of a corrective action plan, appropriate to the audit findings, and may remove the note only after the corrective action plan has been fully implemented.

(5) implement the following as a part of the pharmacovigilance system:

a) Employing at least one person as the qualified person responsible for pharmacovigilance continuously without interruption, ensuring that the functions of the qualified person are fulfilled in his or her absence by a deputy who has the same qualifications. The qualified person responsible for pharmacovigilance and his or her deputy may not have any marketing or sales roles or responsibilities in conducting their pharmacovigilance duties.

b) If several marketing authorization holders functioning under a partnership framework operate a common pharmacovigilance system, a common qualified person responsible for pharmacovigilance with a deputy may be appointed. However, these persons should not have any other roles other than that of the qualified person responsible for pharmacovigilance.

c) Notifying the Agency of the name, professional background and 24/7 contact details of the persons appointed as the qualified person responsible for pharmacovigilance and his or her deputy within seven days of their appointment.

ç) Notifying the Agency in the event of the replacement of the qualified person responsible for pharmacovigilance or his or her deputy as described under point c) above, after appointing a replacement within three months.

d) Ensuring that the qualified person responsible for pharmacovigilance and his or her deputy attend the basic training program on pharmacovigilance provided by the Agency. Supporting attendance to other pharmacovigilance training also, to ensure their knowledge remains up-to-date.

e) Preparing, maintaining and, upon request, presenting the Agency with a pharmacovigilance system master file.

f) Preparing and updating, where necessary, the risk management system with specified and potential risks of the medicinal product, and as required by post-authorization safety data. Monitoring pharmacovigilance data to detect any new risks, or a change in the existing risks or in the risk-benefit balance of the medicinal product, and informing the Agency about any changes.

g) Monitoring the outcome of actions implemented as part of the risk management plan.

ğ) Ensuring and maintaining a record of training of personnel on pharmacovigilance.

(6) may be exempted from the requirement to employ a qualified person responsible for pharmacovigilance, if outsourcing its pharmacovigilance roles entirely. However, if only some of the pharmacovigilance roles are outsourced to a contract pharmacovigilance service provider, the marketing authorization holder must employ a qualified person responsible for pharmacovigilance continuously on an uninterrupted basis. The responsibility to ensure complete and accurate operability of the pharmacovigilance system, including the pharmacovigilance system master file, always rests with the marketing authorization holder.

(7) appends a standard wording to the summary of product characteristics, instructing healthcare providers to report any suspected adverse reactions to TÜFAM.

(8) appends a standard wording to the package leaflet, asking consumers to report any suspected adverse reactions to a healthcare professional or directly to TÜFAM.

(9) for medicinal products included in the additional monitoring list, appends an inverted black equilateral triangle in the summary of product characteristics, with the following wording thereunder: “This medicine is subject to additional monitoring. The triangle will allow quick identification of new safety information. Healthcare professionals are expected to report any suspected adverse reactions to TÜFAM. See section 4.8 How to report adverse reactions.” A similar statement is also included in the package leaflet and promotional materials, with a note inserted in the electronic prescription module that the medicinal product is subject to additional monitoring.

(10) immediately notifies the Agency in the event the market supply of the product has been suspended or the marketing authorization has been withdrawn, or is intended to be withdrawn based on safety concerns.

(11) responds fully and without delay to any requests communicated by the Agency according to this Regulation.

(12) assures the accuracy and currency of any pharmacovigilance information or documents submitted to the Agency, and bear any applicable legal implications. Any inaccuracies in the information or documents submitted are subject to penalization according to Turkish Penal Code #5237 dated 26.09.2004.

Obligations of healthcare professionals

ARTICLE 6 – (1) Spontaneous reporting to TÜFAM of adverse reactions to drugs occurring in patients is a professional responsibility of the healthcare professional observing such reactions, and must be performed according to Article 21 below.

Obligations of healthcare institutions and organizations

ARTICLE 7 – (1) **(Amended clause:OG-21/7/2022-31899)** The provincial health director shall appoint the head or deputy head of department of the provincial health directorate as the pharmacovigilance provincial responsible person and shall notify the name and contact information of this person to the Agency. To ensure most accurate reporting of adverse drug reactions to TÜFAM at the earliest possibility, hospitals will establish and operate an internal pharmacovigilance system according to this Regulation.

(2) To ensure flow of information to TÜFAM, hospital administrators will appoint a pharmacovigilance contact point, and report this person's name, professional background and contact details to the Agency and the provincial officer for pharmacovigilance.

Agency's roles

ARTICLE 8 – The Agency

(1) uses a pharmacovigilance system to gather information on drug-related risks. Collaborates with contract pharmacovigilance service providers where necessary to reduce the risks from drug use.

(2) conducts activities, encouraging consumers and healthcare professionals to report any suspected adverse reactions that they encounter to TÜFAM, and may delegate this function to organizations representing patients' or healthcare professionals' interests.

(3) records suspected adverse reactions occurring in Turkey, reported by healthcare professionals or consumers, and forwards them to the World Health Organization's Center for Drug Monitoring.

(4) relays any reported cases of suspected adverse reactions to the marketing authorization holder within 15 days after the reporting date.

(5) may require healthcare professionals to bear specific obligations to ensure safe use of the medicinal product.

(6) notifies the marketing authorization holder and relevant international organizations regarding any actions taken as a result of investigations.

(7) organizes basic training programs on pharmacovigilance.

(8) creates and updates, where necessary, a list of medicinal products subject to additional monitoring, taking into consideration international practices. Removes the medicinal product from the list five years after it has been authorized in Turkey, or may prolong this timeframe. The Agency may also list medicinal products whose use requires the implementation of a risk management system.

(9) may require the marketing authorization holder or applicant to submit a risk management system should any factors emerge that can affect the risk-benefit balance of a medicinal product, whether authorized or pending authorization.

(10) assesses the updates to the risk management plan, and monitors the outcome of risk minimization actions.

(11) may require the marketing authorization holder to submit data which shows that the product's risk-benefit balance remains favorable, to enable continuous evaluation of the risk-benefit balance.

(12) may require the marketing authorization holder to submit the pharmacovigilance system master file, in which case a copy of this file must be delivered to the Agency within seven days.

CHAPTER THREE
Pharmacovigilance System Master File, Pharmacovigilance Documents Required for Marketing Authorization

Pharmacovigilance documents required for marketing authorization application

ARTICLE 9 – (1) The marketing authorization holder must submit an overview of the pharmacovigilance system while applying for marketing authorization. The overview of the pharmacovigilance system must comprise the following information:

a) A document showing that the marketing authorization holder has appointed the qualified person responsible for pharmacovigilance.

b) Contact details of the qualified person responsible for pharmacovigilance.

c) A signed statement issued by the marketing authorization holder, that the qualified person responsible for pharmacovigilance has the necessary qualifications for fulfilling the pharmacovigilance roles and responsibilities.

ç) A statement that the medicinal product has a pharmacovigilance system master file.

(2) In any of the cases listed in the seventh paragraph of Article 22 below, a risk management must be submitted with the application.

Structure of the pharmacovigilance system master file

ARTICLE 10 – (1) The information in the pharmacovigilance system master file will completely and accurately reflects the pharmacovigilance system in place.

(2) The marketing authorization holder may, where appropriate, use separate pharmacovigilance systems for different categories of medicinal products. Each such system will be described in a separate pharmacovigilance system master file.

Content of pharmacovigilance system master file

ARTICLE 11 – (1) The pharmacovigilance system master file will contain at least the items listed in this article. The following information relating to the qualified person responsible for pharmacovigilance:

a) a description of the responsibilities demonstrating that the qualified person responsible for pharmacovigilance has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance with pharmacovigilance tasks and responsibilities.

b) professional background of the qualified person responsible for pharmacovigilance.

c) contact details of the qualified person responsible for pharmacovigilance.

ç) details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance.

(2) a description of the organizational structure of the marketing authorization holder, including the list of the sites where specific pharmacovigilance activities are undertaken, such as individual case safety report collection, evaluation, safety database case entry, periodic risk-benefit assessment report production, signal detection and analysis, risk management plan management, pre- and post-authorization study management, and management of safety variations to the terms of a marketing authorization.

(3) a description of the location of, functionality of and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose.

(4) a description of data handling and recording and of the process used for each of the following pharmacovigilance activities:

a) the continuous monitoring of the risk-benefit balance of the medicinal products, the result of that monitoring and the decision-making process for taking appropriate measures.

b) monitoring of the risk management systems and of the outcome of risk minimization measures.

c) collection, assessment and reporting of individual case safety reports.

ç) drafting and submission of periodic risk-benefit assessment reports.

d) procedures for communicating safety concerns and safety variations to the summary of product characteristics and package leaflet to healthcare professionals and the general public.

(5) a description of the quality system for the performance of pharmacovigilance activities, including all of the following elements:

a) a description of the management of human resources referred to in Article 26, including a description of the organizational structure established for the performance of pharmacovigilance activities with a reference to the location of qualification records of the personnel, a summary description of the training system, including a reference to the location of training files, and instructions on critical processes.

b) a description of the record management system referred to in Article 28, including the location of the documents used for pharmacovigilance activities.

c) a description of the system for monitoring the performance of the pharmacovigilance system and for compliance with Article 27 requirements.

(6) where applicable, a description of the activities or services conducted by the marketing authorization holder through a contract pharmacovigilance service provider.

Content of the annex to the pharmacovigilance system master file

ARTICLE 12 – (1) The pharmacovigilance system master file will have an annex containing the following documents:

a) a list of medicinal products covered by the pharmacovigilance system master file, including the name of the medicinal product, the international non-proprietary name (INN) of the active substance(s), and the countries in which the authorization is valid.

b) a list of written policies and procedures established for the purpose of complying with the first paragraph of Article 27.

c) a list of the contracts with contract pharmacovigilance service providers, including the names of relevant medicinal products and documents.

ç) a list of all scheduled and completed audits.

d) where applicable, a list of other pharmacovigilance system master files held by the same marketing authorization holder.

e) an electronic logbook.

Ensuring the master file is kept up-to-date

ARTICLE 13 – (1) The marketing authorization holder will keep the pharmacovigilance system master file up to date and, where necessary, revise it to take account of experience gained, of technical and scientific progress and of regulatory amendments.

(2) The marketing authorization will indicate the last update date on the pharmacovigilance system master file and its annex, giving each update number.

(3) Any deviations from the pharmacovigilance procedures, their impact and their management will be documented in the pharmacovigilance system master file until resolved.

Form of the documents contained in the pharmacovigilance master file

ARTICLE 14 – (1) Pharmacovigilance system master file documents will be complete and legible. Where appropriate, information may be provided in the form of charts or flow diagrams. All documents will be indexed and archived so as to ensure their accurate and ready retrieval.

(2) The particulars and documents of the pharmacovigilance system master file may be presented in modules in accordance with the system described in the applicable guidance.

(3) The pharmacovigilance system master file may be stored in electronic form provided that the media used for storage remain readable over time and a clearly arranged printed copy can be made available for audits and inspections.

(4) The marketing authorization holder will record in the electronic logbook any alteration of the content of the pharmacovigilance system master file made within the last five years, with the exception of the information referred to in Article 12 and in points (b), (c) and (ç) of Article 11. The marketing authorization holder will indicate in the electronic logbook the date, the person responsible for the alteration, and, where appropriate, the reason for the alteration.

Availability and location of the pharmacovigilance system master file

ARTICLE 15 – (1) The pharmacovigilance system master file will be located at the site where pharmacovigilance activities are performed.

(2) The marketing authorization holder will ensure that the qualified person for pharmacovigilance has permanent access to the pharmacovigilance system master file.

(3) The pharmacovigilance system master file will be permanently and immediately available for inspection at the site where it is kept.

(4) The pharmacovigilance system master file must be directly accessible also when it is kept in electronic form in accordance with the third paragraph of Article 14.

(5) The Agency may require the marketing authorization holder to submit a copy of the logbook at regular intervals.

CHAPTER FOUR
Suspected Adverse Reaction Reports

Content of the suspected adverse reaction reports

ARTICLE 16 – (1) A TÜFAM reporting form will be used for submitting suspected adverse reaction reports to TÜFAM.

(2) Marketing authorization holders will ensure that adverse reaction reports are as complete as possible and will communicate the updates of those reports to TİFAM in an accurate and reliable manner. A report will include at least an identifiable reporter, an identifiable patient, a suspected adverse reaction and a suspected medicinal product.

(3) Marketing authorization holders will record the details necessary for obtaining follow-up information on adverse reaction reports. The follow-up of reports will be adequately documented.

(4) When reporting suspected adverse reactions, marketing authorization holders will provide all available information on each individual case, including the following:

a) report type, date, and a case reference number; the date on which the report was first received from the source and the date of receipt of the most recent information, and other additional documents, if applicable;

b) **(Amended:OG-21/7/2022-31899)** Descriptive information for the reporter, including professional qualifications.

c) information identifying the patient, and parent in the case of a parent-child report, including age at the time of the onset of the first reaction, age group, weight, height, or gender, last maternal menstrual date and/or gestation period at time of exposure, and gestational age if the reaction was observed in the fetus;

ç) relevant medical history and concurrent conditions;

d) the name of the medicinal product(s) suspected to be related to the occurrence of the adverse reaction, including interacting medicinal products or, where the name is not known, the active substance and any other characteristics that help identify the medicinal product, including the name of the marketing authorization holder, marketing authorization number, pharmaceutical form and routes of administration, indications for use, dose administered, start date and end date of administration, actions taken with the medicinal product after the adverse reaction occurred, effect of the dechallenge and rechallenge;

e) In the event of suspected quality problems with a product, the batch number, expiration date, and a description of the quality concern;

f) **(Amended:OG-21/7/2022-31899)** Lot numbers for biological and biotechnological products.

g) concomitant medicinal products, which are not suspected to be related to the occurrence of the adverse reaction and relevant past medical therapies administered to the patient or the parent;

ğ) start date and end date of the suspected adverse reactions or duration, seriousness, outcome of the suspected adverse reactions at the time of last observation, time intervals between suspect medicinal product administration and start of adverse reaction, the original reporter's words or short phrases used to describe the reaction(s);

h) results of tests and procedures relevant to the adverse reaction;

ı) date and cause of death, including autopsy-determined causes, in the event of death of the patient;

i) for serious adverse reactions, a case narrative, providing all relevant information in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained;

j) reasons for nullifying or amending an adverse reaction report.

Literature reports

ARTICLE 17 – (1) The marketing authorization holder will submit to TÜFAM a copy of any national or international article involving an adverse reaction that occurred in Turkey, or an abstract of the article in Turkish, if published in a language other than Turkish. Upon TÜFAM's request, a full translation of the article will be submitted.

CHAPTER FIVE
Periodic Risk-Benefit Assessment Reports

Content of periodic risk-benefit assessment reports

ARTICLE 18 – (1) The periodic risk-benefit assessment report will be based on all available data related to the medicinal product's risks and benefits, including information on off-label use and data from clinical studies, and will focus on new information which has emerged since the data-lock point of the last periodic risk-benefit assessment report to provide a scientific assessment of the medicinal product's risk-benefit balance.

(2) The periodic risk-benefit assessment report will provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. The exposure estimate will be accompanied by a qualitative and quantitative analysis of actual use, which will indicate, where appropriate, how actual use differs from the

indicated use based on all data available to the marketing authorization holder, including the results of observational or drug utilization studies.

(3) The periodic risk-benefit assessment report will contain the results of assessments of the effectiveness of risk minimization activities relevant to the risk–benefit assessment.

(4) Marketing authorization holders will not be required to include systematically detailed listings of individual cases, including case narratives, in the periodic risk-benefit assessment report. However, they will provide case narratives in the relevant risk evaluation section where relevant to the scientific analysis of a signal or safety concern.

(5) Based on the evaluation of the cumulative safety data and risk-benefit analysis, the marketing authorization holder will draw conclusions in the periodic risk-benefit assessment report as to the need for changes and/or actions, including implications for the approved summary of product characteristics for the medicinal product for which the periodic risk-benefit assessment report is submitted.

(6) Unless otherwise specified by the Agency, a single periodic risk-benefit assessment report will be prepared for all medicinal products containing the same active substance and authorized for one marketing authorization holder. The periodic risk-benefit assessment report will cover all indications, routes of administration, dosage forms and dosing regimens, irrespective of whether authorized under different names and through separate procedures. Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen will be presented in a separate section of the periodic risk-benefit assessment report and any safety concerns will be addressed accordingly.

(7) If the substance that is the subject of the periodic risk-benefit assessment report is also authorized as a component of a fixed-dose combination medicinal product, either a separate periodic risk-benefit assessment report will be submitted for the combination of active substances authorized for the same marketing authorization holder, with cross-references to the single-substance periodic risk-benefit assessment reports, or the combination data will be submitted within one of the single- substance periodic risk-benefit assessment reports.

(8) The periodic risk-benefit assessment report will be issued in the format provided in Appendix 1.

CHAPTER SIX
Risk Management Plans

Format and content of risk management plans

ARTICLE 19 – (1) The risk management plan established by the marketing authorization holder will contain the following elements:

a) a characterization of the safety profile of the medicinal products concerned;

b) an indication of how to characterize further the safety profile of the medicinal products concerned;

c) a documentation of measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those measures;

(2) Products containing the same active substance and belonging to the same marketing authorization holder may be subject, where appropriate, to the same risk management plan.

(3) Where a risk management plan refers to post-authorization studies, it will indicate whether those studies are initiated, managed or financed by the marketing authorization holder voluntarily or pursuant to obligations imposed by the competent authorities. All post-authorization obligations will be listed in the summary of the risk management plan together with a timeframe.

(4) The risk management plan will be issued in the format provided in Appendix 2.

Updates of the risk management plan

ARTICLE 20 – (Amended:OG-21/7/2022-31899)

(1) Where the marketing authorization holder updates the risk management plan, the holder shall archive the updated version of the risk management plan with a separate version number and date. If the updates made require additional pharmacovigilance or additional risk minimization activities or changes in existing activities, the holder shall immediately submit them to the Agency.

CHAPTER SEVEN
Reports Submitted to the Agency and Assessment of Reports

Reports by healthcare professionals

ARTICLE 21 – (1) Healthcare professionals will report any adverse reactions which result from, or may be associated with the use of a medicinal product to TÜFAM within fifteen days, directly or through the pharmacovigilance contact point established at their healthcare institution. Reports by marketing authorization holders

ARTICLE 22 – The marketing authorization holder (1) maintains and archives a detailed record of all suspected adverse reactions related to the medicinal product, occurring during post- authorization safety studies or spontaneously reported by patients or healthcare professionals in Turkey or other countries where the product is marketed;

(2) reports all suspected serious adverse reactions occurring in Turkey to TÜFAM within fifteen days after becoming aware of such information. It also gathers follow-up information on these reports, and forwards it to TÜFAM within fifteen days;

(3) if reports received from other countries where the product is marketed alters the medicinal product's known risk-benefit balance, informs TÜFAM immediately after receiving such information;

(4) monitors all scientific and medical literature, including those involving data on Turkey, as an important information source for suspected adverse reaction case reports, and reports any serious adverse reactions occurring in Turkey to TÜFAM within fifteen days;

(5) develops methodologies to obtain true and verifiable data for the scientific assessment of suspected adverse reaction reports;

(6) if it is suspected that an infectious agent is transmitted via a medicinal product, notifies the Agency immediately after becoming aware of such information;

(7) submits a risk management plan

a) during marketing authorization application for medicinal products containing a new active substance, biotechnological medicinal products, biosimilar medicinal products and generic medicinal products where additional risk minimization activities were required for the original medicinal product;

b) where a new manufacturing process is used for an authorized biotechnology-derived or biosimilar medicinal product;

c) when required by the Agency before or after authorization;

ç) upon the initiative of the applicant/marketing authorization holder in the event of a safety concern identified at any stage of a medicinal product's lifecycle.

(8) **(Amended:OG-21/7/2022-31899)** The holder shall prepare periodic benefit/risk assessment reports in accordance with the list of European Union reference date and frequency of submission after obtaining a marketing authorisation in Türkiye. In case the active substance of the medicine is not included in this list, the holder shall prepare it every six months for the first two years, once a year for the next two years, and every three years following the extension of the marketing authorisation validity period and submit it immediately upon the request of the Agency.

(9) **(Amended:OG-21/7/2022-31899)** The holder shall submit periodic benefit/risk assessment reports to the Agency in accordance with the provision related to the submission schedule specified in the Regulation on the Marketing Authorization of Medicinal Products for Human Use published in the Official Gazette dated 11/12/2021 and numbered 31686 during the extension of the marketing authorization period of the medicines.

(10) When the marketing authorization holder is changed for a medicinal product previously authorized by the Agency, the submission periods of pharmacovigilance data are maintained based on the first marketing authorization date.

(11) continues to regularly monitor the safety of medicinal products by preparing periodic risk-benefit assessment reports and makes an application to the Agency for a variation to the terms of the marketing authorization in the event of new safety information that impacts on the product's risk- benefit balance or summary of product characteristics/package leaflet.

(12) gives advance or simultaneous notice to the Agency when publicizing information on pharmacovigilance concerns regarding the use of its medicinal products. The marketing authorization holder assures that this information is accurate and not misleading.

Assessment by the Agency

ARTICLE 23 – (1) The Agency may require the marketing authorization holder to fulfill the following obligations. In that case, the provisions of the Clinical Trials Regulation, published in Official Gazette #28617 dated 13.04.2013, apply.

a) Conducting a post-authorization safety study, if concerns arise as to the risks of an authorized medicinal product, or a joint study by marketing authorization holders, if similar concerns exist for several medicinal products.

b) Conducting a post-authorization efficacy study, if the understanding or clinical methodology of the disease indicate significant reconsideration of the previous efficacy assessments.

(2) The Agency performs a scientific assessment of all the data using the pharmacovigilance system, and considers risk minimization and prevention options.

(3) The Agency considers the following regarding authorized medicinal products:

a) monitoring the results of risk minimization measures implemented under the risk management plan;

b) assessing the updates to the risk management system;

c) performing relevant assessments, including preparing a periodic risk-benefit assessment report, to determine whether new risks exists or existing risks have changed or risks impact on the risk-benefit balance.

(4) The Agency and the marketing authorization holder notify the other in the event new risks emerge or changes occur in the risk-benefit balance.

(5) **(Appended:OG-21/7/2022-31899)** While making its own decisions about medicine safety, the Agency may take into account the evaluations made by other medicine authorities or regional or international organizations with comparable standards within the scope of reliance and share information.

Post-assessment actions

ARTICLE 24 – (1) After the assessment, the Agency initiates the following actions, as appropriate to the pharmacovigilance situation, and notifies the marketing authorization holder:

a) Conducting a post-authorization study.

b) Implementing risk minimization measures.

c) Suspending, revoking or rejecting the request for extending validity period of the marketing authorization.

ç) Prohibiting procurement of the medicinal product.

d) Changing product information, e.g. addition of a new contraindication, reduction of the recommended dose, introduction of indication restrictions.

CHAPTER EIGHT
Requirements for the Quality Systems for the Performance of Pharmacovigilance Activities

General principles for the quality system

ARTICLE 25 – (1) The marketing authorization holder will use a quality system that is adequate and effective for the performance of its pharmacovigilance activities.

(2) The quality system will cover organization structure, responsibilities, procedures, processes and resources, appropriate resource management, compliance management and record management.

(3) The quality system will be based on all of the following activities:

a) quality planning, involving establishment of structures and planning of integrated and consistent processes;

b) quality adherence, involving the carrying out of tasks and responsibilities in accordance with quality requirements;

c) quality control and assurance, involving the monitoring and evaluation of how effectively the structures and processes have been established and how effectively the processes are being carried out;

ç) quality improvements, involving the correction and improvement of the structure and processes, where necessary.

(4) All elements, requirements and provisions adopted for the quality system will be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.

Management of human resources

ARTICLE 26 – (1) The marketing authorization holder will assemble a competent and appropriately qualified and trained personnel for the performance of pharmacovigilance activities, ensuring that the qualified person responsible for pharmacovigilance has adequate theoretical and practical knowledge for the performance of pharmacovigilance activities.

(2) The duties of the managerial and supervisory staff, including the qualified person responsible for pharmacovigilance, will be defined in job descriptions. Their hierarchical relationships will be defined in an organizational chart. The marketing authorization holder will ensure that the qualified person responsible for pharmacovigilance has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities.

(3) All personnel involved in the performance of pharmacovigilance activities will receive initial and continued training in relation to their role and responsibilities. The marketing authorization holder will keep training plans and records for documenting, maintaining and developing the competences of personnel and make them available for audit or inspection.

(4) The marketing authorization holder will provide appropriate instructions on the processes to be used in case of urgency, including business continuity.

Compliance management

ARTICLE 27 – (1) The marketing authorization holder will implement specific quality system procedures to ensure all of the following:

a) the continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and taking of appropriate measures;

b) subjecting of all information on the risks of medicinal products to scientific evaluation;

c) submission of accurate and verifiable data on serious adverse reactions to TÜFAM within the timeframes specified in the second, third and fourth paragraphs of Article 22;

ç) the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals;

d) effective communication with the Agency, including communication on new risks or changed risks, the pharmacovigilance system master file, risk management systems, risk minimization measures, periodic risk-benefit assessment reports, corrective and preventive actions, and post- authorization studies;

e) the update of product information based on continuous monitoring of scientific data and postings on the Agency's official website;

f) appropriate communication of relevant safety information to healthcare professionals and patients.

(2) Where a marketing authorization holder has delegated a contract pharmacovigilance service provider with some of its pharmacovigilance tasks, it will retain responsibility for ensuring that an effective quality system is applied in relation to those tasks.

Record management and data retention

ARTICLE 28 – (1) Marketing authorization holders will maintain a record of all pharmacovigilance activities and ensure that the records are handled and stored so as to allow for accurate reporting, interpretation and verification of that information.

(2) Marketing authorization holders will put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents as well as the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process.

(3) Marketing authorization holders will establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

(4) Marketing authorization holders will arrange for the elements referred to in Article 11 to be kept for at least five years after the system as described in the pharmacovigilance system master file has been formally terminated. Pharmacovigilance data and documents relating to individual medicinal products will be retained as long as the product is authorized and for at least 10 years after the marketing authorization has ceased to exist.

Audit

ARTICLE 29 – (1) Risk-based audits of the quality system will be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in Articles 25, 26, 27 and 28 and to determine its effectiveness. Those audits will be conducted by individuals who have no direct involvement in or responsibility for the matters or processes being audited.

(2) Corrective actions, including a follow-up audit of deficiencies, will be taken where necessary. The audit report will be sent to the management responsible for the matters audited. The dates and results of audits and follow-up audits will be documented.

CHAPTER NINE
Miscellaneous and Final Provisions

Off-label use and occupational exposure

ARTICLE 30 – (1) Adverse reactions to medicinal products authorized by the Agency for off-label use or named patient use, and adverse drug reactions associated with occupational exposure will be reported according to this Regulation. The Agency may require the implementation of risk management, where necessary.

Confidentiality

ARTICLE 31 – (1) The Agency will protect the confidentiality of the identity and address of the patient and the reporting physician in any reports submitted to the Agency. Such information may not be disclosed to anyone except TÜFAM personnel for any reason whatsoever. Marketing authorization holders, healthcare institutions and organizations and healthcare professionals must also adhere to the same confidentiality requirement.

Inspection

ARTICLE 32 – (1) Marketing authorization holders, healthcare institutions and organizations, contract pharmacovigilance service providers and other relevant entities will be subject to inspection by the Agency for their activities falling within the scope of this Regulation.

(2) The Agency may conduct a pre-authorization inspection to ensure that the marketing

authorization is properly and successfully implementing a pharmacovigilance system.

(3) The organizations and institutions referenced in this Article will have appropriate measures in place to ensure proper conduct of inspections, and the availability of any information or documents related to the subject matter of inspection, during the inspection.

(4) Inspections will be conducted according to applicable guidelines.

Regulatory penalties

ARTICLE 33 – (Amended:OG-21/7/2022-31899) (1) Marketing authorization holders and contracted pharmacovigilance service organizations, who are found to be in violation of the provisions of this Regulation as a result of the inspections and examinations carried out by the Agency, are given time to correct the deficiencies in accordance with the nature of the detected violation. If the violation is not remedied at the end of the given period;

a) For contracted pharmacovigilance service organizations depending on the nature of the violation restriction of activities, suspension or cancellation of permit certificate,
b) For marketing authorisation holders depending on the nature of the violation, prevention of pharmaceutical track and trace system notification, suspension of product movements, suspension or cancellation of the marketing authorisation of the medicine may be imposed.

(2) Deficiencies detected at healthcare institutions or organizations during inspections will be rectified as instructed by the Agency.

Guideline

ARTICLE 34 – (1) The Agency will issue specific guidelines to provide guidance and clarity for the implementation of this Regulation.

Repealed regulation

ARTICLE 35 – (1) The Regulation on Safety Monitoring and Assessment of Human Medicinal Products, published in Official Gazette #25763 dated 22.03.2005, is hereby repealed.

Transitional period for authorized medicinal products to be listed for additional monitoring

TRANSITIONAL ARTICLE 1 – (1) For authorized medicinal products which will be listed for additional monitoring according to Article 8 of this Regulation, compliance with the ninth paragraph of Article 5 must be ensured within six months after the posting of the list by the Agency.

Effectiveness

ARTICLE 36 – (1) Of this Regulation:

a) point (e) of the fifth paragraph of Article 5 will enter into force one year after the publication date hereof;

b) the eighth paragraph of Article 8 will enter into force three months after the publication date hereof;

c) all the other articles will enter into force on the publication date hereof.

Enforcement

ARTICLE 37 – (1) This Regulation will be enforced by the President of Turkish Medicines and Medical Devices Agency.

Appendix 1

Periodic Risk-Benefit Assessment Report

The periodic risk-benefit assessment report will consist of the following modules:

Part I: Title page including signature

Part II: Executive summary

Part III: Table of contents.

1. Introduction.
2. Worldwide marketing authorization status.
3. Actions taken in the reporting period for safety reasons.
4. Changes to reference safety information.
5. Estimated exposure and use patterns.

5.1 Cumulative exposure in clinical trials.

5.2 Post-marketing cumulative and reporting period patient exposure.

6. Data in summary tabulations.

6.1 Reference information.

6.2 Cumulative summary tabulations of serious adverse events from clinical trials.

6.3 Cumulative and reporting period summary tabulations from post-marketing data sources.

7. Summaries of significant findings from clinical trials during the reporting period.

7.1 Completed clinical trials.

7.2 Ongoing clinical trials.

7.3 Long-term follow-up.

7.4 Other therapeutic use of the medicinal product.

7.5 New safety data related to fixed combination therapies.

8. Findings from non-interventional studies.
9. Information from other clinical trials and sources.
10. Non-clinical data.
11. Literature.
12. Other periodic reports.
13. Lack of efficacy in controlled clinical trials.
14. Late-breaking information.
15. Overview on new, ongoing or closed signals.
16. Signal and risk evaluation.

16.1 Summaries of safety concerns.

16.2 Signal evaluation.

16.3 Evaluation of risks and new information.

16.4 Characterization of risks.

16.5 Effectiveness of risk minimization (if applicable).

17. Benefit evaluation.

17.1 Important baseline efficacy and effectiveness information from clinical trials and post-marketing experience.

17.2 Newly identified information on efficacy and effectiveness from clinical trials and post-marketing experience.

17.3 Characterization of benefits.

18. Integrated risk-benefit analysis for authorized indications.

18.1 Risk-benefit context (medical need and important alternatives).

18.2 Risk-benefit analysis evaluation.

19. Conclusions and actions.
20. Appendixes to the periodic risk-benefit assessment report.

Appendix 2

Risk Management Plans
Format of the risk management plan

The risk management plan will consist of the following modules:

- Part I: Product(s) overview.
- Part II: Safety specification.
  - Module I: Epidemiology of the indications and target populations.
  - Module II: Non-clinical part of the safety specification.
  - Module III: Clinical trial exposure.
  - Module IV: Populations not studied in clinical trials.
  - Module V: Post-authorization experience.
  - Module VI: Additional requirements for the safety specification, asked by other health authorities.
  - Module VII: Identified and potential risks.
  - Module VIII: Summary of the safety concerns.
- Part III: Pharmacovigilance plan (including post-authorization safety studies).
- Part IV: Plans for post-authorization efficacy studies.
- Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities).
- Part VI: Summary of the risk management plan.
- Part VII: Appendixes.