Guideline on Good Pharmacovigilance Practices

APPENDIX I – Definitions

Turkish Medicines and Medical Devices Agency
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EU Reference date, Union reference date
For medicinal products containing the same active substance or the same combination of active substances, the date of the first marketing authorization in the EU of a medicinal product containing that active substance or that combination of active substances; or if this date cannot be ascertained, the earliest of the known dates of the marketing authorizations for a medicinal product containing that active substance or that combination of active substances.

Adverse event (AE), Adverse experience
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction, Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect
A response to a medicinal product which is noxious and unintended [Regulation on the Safety of Medicinal Products, Art. 4(1)a].

'Response' in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Minimum criteria for reporting
For the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a case are: an identifiable reporter, an identifiable patient, an adverse reaction and a suspect medicinal product.

Unexpected adverse reaction
An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics. [Regulation on the Safety of Medicinal Products, Art. 4(1)c].

This includes class-related reactions which are mentioned in the summary of product characteristics (SmPC) but which are not specifically described as occurring with this product.

Individual case safety report (ICSR), Adverse (drug) reaction report
Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time.

Serious adverse reaction
An adverse reaction which results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [Regulation on the Safety of Medicinal Products, Art. 4(1)d].

The characteristics/outcomes during an adverse reaction should be taken into account when deciding the seriousness of a case. For example, the term 'life-threatening' refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions. Some medical events might jeopardize the patient or require intervention to prevent one of the other outcomes listed above. These types of important medical events should be considered 'serious.' Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Ongoing signal
In periodic benefit/risk assessment reports, a signal that remains under assessment at the data lock point.

This definition is also applicable to periodic safety update reports.

Overdose
Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the Agency-authorized summary of product characteristics (SmPC). Clinical judgment should always be applied to determine whether overdosing has occurred.

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

It is defined as critical gaps in knowledge for specific safety issues or populations that use the marketed product [International Conference on Harmonization (ICH)].

Pharmacovigilance
Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem [Regulation on the Safety of Medicinal Products, Art. 4(1)e].

In line with this general definition, underlying objectives of pharmacovigilance in accordance with the applicable legislation are:

- preventing harm from adverse reactions in humans arising from the use of authorized medicinal products within or outside the terms of marketing authorization or from occupational exposure; and
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

Pharmacovigilance system
A system used by marketing authorization holders, applicants, the Agency and other organizations to fulfill the tasks and responsibilities listed in the Regulation on the Safety of Medicinal Products and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance [Regulation on the Safety of Medicinal Products, Art. 4(1)ğ].

Pharmacovigilance system master file
A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized medicinal products [Regulation on the Safety of Medicinal Products, Art. 4(1)h].

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

Quality system of a pharmacovigilance system
The organizational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management. The quality system is a part of the pharmacovigilance system.

Company core safety information (CCSI)
For medicinal products, all relevant safety information contained in the company core data sheet prepared by the marketing authorization holder and which the marketing authorization holder requires to be listed in all countries where the company markets the product, except when the regulatory authority specifically requires a modification.

It is the reference information by which 'listed' and 'unlisted' are determined for the purposes of periodic reporting for marketed products, but not by which 'expected' and 'unexpected' are determined for expedited reporting.

Company core data sheet (CCDS)
For medicinal products, a document prepared by the marketing authorization holder containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.

Safety issue, Safety concern
An important identified risk, important potential risk or missing information.

Target population (treatment), Treatment target population
The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorized product information.

Medicinal product
Any substance or combination of substances presented as having properties for treating or preventing disease in human beings or which may be used in human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action [Regulation on the Safety of Medicinal Products, Art. 4(1)i].

Misuse of a medicinal product
Use of a medicinal product intentionally and inappropriately not in accordance with the authorized product information.

Risks related to use of a medicinal product
Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment.

Abuse of a medicinal product
Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [Regulation on the Safety of Medicinal Products, Art. 4(1)j].

Misuse of a medicinal product for illegal purposes
Misuse for illegal purposes is misuse with the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault.

Quality requirements
Those characteristics of a system that are likely to produce the desired outcome, or quality objectives.

Quality improvements
Correcting and improving the structures and processes where necessary. This applied for the purpose of fulfilling quality requirements.

Quality control and assurance
Monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out.

This applies for the purpose of fulfilling quality requirements.

Quality planning
Establishing structures and planning integrated and consistent processes.

This applies for the purpose of fulfilling quality requirements.

Quality adherence
Carrying out tasks and responsibilities in accordance with quality requirements.

Closed signal
In periodic benefit/risk assessment reports, a signal for which an evaluation was completed during the reporting interval.

This definition is also applicable to periodic safety update reports.

Crisis
In the context of this guideline, a crisis is defined as a situation where, after assessment of the associated risks, urgent and coordinated action is required between the Agency and the marketing authorization holder.

Occupational exposure
An exposure to a medicinal product as a result of one's professional or non-professional occupation.

Important event
A situation where an event occurs or new information arises, irrespective whether this is in the public domain or not, in relation to (an) authorized medicinal product(s) which could have a serious impact on public health.

An important event may be related to quality, efficacy or safety concerns, but most likely to safety and/or quality (and possibly subsequent supply shortages). In addition, situations that do not seem at a first glance to have a serious impact on public health, but are in the public domain – subject of media attention or not – and may lead to serious public concerns about the product, may also need to be considered as important events. Likewise, other situations which might have a negative impact on the appropriate use of a medicinal products (e.g. resulting in patients stop taking their medicine) may fall within this definition.

Important identified risk and important potential risk
An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.

What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.

Periodic benefit/risk assessment report (PBRAR)
Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorization holder at defined time points during the post-authorization phase.

Periodic benefit/risk assessment reports should follow the format described in Module II.

Potential risk
An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.

Examples include:

- non-clinical toxicological findings that have not been observed or resolved in clinical studies;
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group, on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship;
- a signal arising from a spontaneous adverse reaction reporting system;
- an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.

Reference safety information
In periodic benefit/risk assessment reports for medicinal products, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the marketing authorization holder and which the marketing authorization holder requires to be listed in all countries where it markets the product, except when the regulatory authority specifically requires a modification.

It is a subset of information contained within the marketing authorization holder's reference product information for the periodic benefit/risk assessment report. Where the reference product information is the company core data sheet, the reference safety information is the company core safety information.

Risk
Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment [Regulation on the Safety of Medicinal Products, Art. 4(1)n].

Risk minimization activity, risk minimization measure, risk mitigation activity
An intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine, or to reduce its severity should it occur.

These activities may consist of routine risk minimization (e.g. product information) or additional risk minimization activities (e.g. healthcare professional or patient communications/educational materials).

Risk management plan (RMP)
A detailed description of the risk management system [Regulation on the Safety of Medicinal Products, Art. 4(1)ö].

To this end, A RMP must identify or characterize the safety profile of the medicinal product(s) concerned, indicate how to characterize further the safety profile of the medicinal product(s) concerned, document measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorization obligations that have been imposed by the Agency as a condition of the marketing authorization.

Risk management system
A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those interventions [Regulation on the Safety of Medicinal Products, Art. 4(1)ö].

Post-authorization safety study (PASS)
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 [Regulation on the Safety of Medicinal Products, Art. 4(1)p].

A post-authorization safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.

Healthcare professional
For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as physicians, pharmacists, dentists, nurses and midwives [Regulation on the Safety of Medicinal Products, Art. 4(1)r].

Direct healthcare professional communication (DHPC)
A letter by which important information is delivered directly to individual healthcare professionals by a marketing authorization holder or by the Agency, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.

DHPCs are not replies to enquiries from healthcare professionals.

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 [Regulation on the Safety of Medicinal Products, Art. 4(1)s].

Signal validation
Process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

Signal management process
Includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritization, signal assessment and recommendation for action.

It comprises a set of activities performed to determine whether, based on an examination of ICSRs, aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks causally associated with an active substance or a medicinal product or whether known risks have changed.

Spontaneous report, Spontaneous notification
An unsolicited communication by a healthcare professional or consumer to the marketing authorization holder or the Agency 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 [Regulation on the Safety of Medicinal Products, Art. 4(1)t].

In this context, an adverse reaction refers to a suspected adverse reaction.

Stimulated reporting can occur in certain situations, such as after a direct healthcare professional communication, a publication in the press or questioning of healthcare professionals by company representatives, and adverse reaction reports arising from these situations are considered spontaneous reports. Reporting can also be stimulated by invitation from patients' or consumers' organizations to their members.

Individual case safety reports from solicited sources
Organized data collection systems, which include clinical trials, non-interventional studies, off-label use or named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance. For the purpose of safety reporting, solicited reports should not be

considered spontaneous but classified as individual case safety reports from studies and therefore should have an appropriate causality assessment by a healthcare professional or the marketing authorization holder.

Completed clinical trial
Study for which a final clinical study report is available.

Identified risk
An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.

Examples include:

- an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group on a parameter of interest, suggests a causal relationship;
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

Adverse reactions included in section 4.8 of the summary of product characteristics (SmPC) are also considered identified risks, unless they are class-related reactions which are mentioned in the SmPC but which are not specifically described as occurring with this product (these would normally be considered as a potential risk).

Consumer
For the purpose of reporting cases of suspected adverse reactions, a person who is not a healthcare professional such as a patient, lawyer, friend or relative/parent/child of a patient [Regulation on the Safety of Medicinal Products, Art. 4(1)v].

Good pharmacovigilance practice (GVP) in Turkey
A set of guidelines for the conduct of pharmacovigilance in the country, applying to marketing authorization holders, contract pharmacovigilance service providers and the Agency.

International birth date
The date of the first marketing authorization for any product containing the active substance granted to any company in any country in the world.

Development international birth date
Date of first approval (or authorization) for conducting an interventional clinical trial in any country.

Validated signal
A signal where the signal validation process of evaluating the data supporting the detected signal has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

Data lock point
For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR.

For a periodic benefit-risk assessment report (PBRAR), the date designated as the cut-off date for data to be included in a PBRAR, based on the international birth date.

The date includes day and month.

Benefit/risk balance
An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health [Regulation on the Safety of Medicinal Products, Art. 4(1)y].

Newly identified signal
In periodic benefit/risk assessment reports, a signal first identified during the reporting interval, prompting further actions or evaluation.

This definition could also apply to a previously closed signal for which new information becomes available in the reporting interval prompting further action or evaluation.

This definition is also applicable to periodic safety update reports.

Audit
A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled.

Audit finding(s)
Results of the evaluation of the collected audit evidence against audit criteria. Audit evidence primarily comprises cumulative information obtained during the course of the audit and is important in that it is necessary for supporting the auditor's assessment.

Audit plan
Description of activities and arrangement for an individual audit.

Audit program
Set of one or more audits planned for a specific timeframe and directed towards a specific purpose.

Audit recommendation
Describes the course of action management might consider to rectify conditions that have gone awry, and to mitigate weaknesses in systems of management control.

Audit recommendations should be positive and as specific as possible. They should also identify who is to act on them.