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3 Guideline on good pharmacovigilance practices (GVP)

4 Annex I - Definitions

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Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu.

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Abuse of a medicinal product

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

Adverse event (AE); synonym: Adverse experience

Any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment [Dir 2001/20/EC Art 2(m)].

An adverse event can therefore be any unfavourable 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; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction

A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)].

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline).

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [DIR 2001/83/EC Art 101(1)]. Conditions of use outside the marketing authorisation include overdose, misuse, abuse and medication errors.

See also Adverse event, Serious adverse reaction, Unexpected adverse reaction, Listed adverse reaction, Unlisted adverse reaction, Overdose, Misuse, Abuse, Medication error, Occupational exposure

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy. This includes clinical trials carried out in either one site or multiple sites, whether in one or more Member State [Dir 2001/20/EC Art 2(a)].

An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form [Dir 2001/20/EC Art 2(d)].

See also Ongoing clinical trial, Completed clinical trial

Closed signal

In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH-E2C(R2) Guideline).

See also Signal

Company core data sheet (CCDS)

A document prepared by the marketing authorisation holder containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product (see Annex IV, ICH-E2C(R2) Guideline).

Company core safety information (CCSI)

All relevant safety information contained in the company core data sheet prepared by the marketing authorisation holder and which the marketing authorisation holder requires to be listed in all countries where the company markets the product, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting (see Annex IV, ICH-E2C(R2) Guideline).

See also Company core data sheet

Completed clinical trial

Study for which a final clinical study report is available (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

See also Clinical trial

Consumer

A person who is not a healthcare professional such as a patient, lawyer, friend or relative/parent/child of a patient (see Annex IV, ICH-E2D Guideline).

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 evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date (see Annex IV, ICH-E2C(R2) Guideline).

For a development safety update report (DSUR), the date designated as the cut-off date for data to be included in a DSUR, based on the development international birth date (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

Date includes day and month (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

See also Periodic safety update report, Development safety update report, International birth date and Development international birth date

Development international birth date (DIBD)

Date of first approval (or authorisation) for conducting an interventional clinical trial in any country (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

Development safety update report (DSUR)

Format and content for periodic reporting on drugs under development (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

EU reference date; synonym: Union reference date

For medicinal products containing the same active substance or the same combination of active substances, the date of the first marketing authorisation 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 authorisations for a medicinal product containing that active substance or that combination of active substances [DIR 2001/83/EC Art 107c(5)].

Good pharmacovigilance practices (GVP) for the European Union

A set of guidelines for the conduct of pharmacovigilance in the EU, drawn up based on Article 108a of Directive 2001/83/EC, by the Agency in cooperation with competent authorities in Member States and interested parties, and applying to marketing authorisation holders in the EU, the Agency and competent authorities in Member States.

Healthcare professional

For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners (see Annex IV, ICH-E2D Guideline).

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 (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

In a clinical trial, the comparator may be placebo, an active substance or non-exposure.

See also Risks related to use of a medicinal product, Important identified risk and Important potential risk, Important missing information

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 (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

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 (see Annex IV, ICH-E2C(R2) Guideline).

See also Risk-benefit balance, Identified risk, Potential risk, Safety concern

Important missing information

Critical gaps in knowledge for specific safety issues or populations that use the marketed product (see Annex IV, ICH-E2C(R2) Guideline).

See also Missing information, Safety concern

Important potential risk

See Important identified risk and Important potential risk

Individual case safety report (ICSR); synonym: 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 [IM Annex I.1.][1].

A valid individual case safety report for expedited reporting shall include at least an identifiable reporter, an identifiable patient, at least one suspect adverse reaction and a suspect medicinal product [IM Annex I.1.].

International birth date (IBD)

The date of the first marketing authorisation for a medicinal product in any country in the world (see Annex IV, ICH-E2C(R2) Guideline).

Investigational drug

Experimental product under study or development. This term is more specific than investigational medicinal product, which includes comparators and placebos (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

See also Clinical trial

Listed adverse reaction

An adverse reaction whose nature, severity, specificity and outcome are consistent with the information in the company core safety information.

Class-related reactions which are mentioned in the company core safety information but which are not specifically described as occurring with this product are not considered as listed.

See also Company core safety information

Medication error

Any unintentional error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.

[1] In the context of a clinical trial, an individual case is the information provided by a primary source to describe suspected unexpected serious adverse reactions related to the administration of one or more investigational medicinal products to an individual patient at a particular point of time.

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 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 [DIR 2001/83/EC Art 1(2)].

Missing information

Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

Misuse

Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorised dose, route of administration, and/or the indication(s) or not within the legal status of its supply (e.g. without prescription for medicinal products subject to medical prescription).

Name of the medicinal product

The name which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder [DIR 2001/83/EC Art 1(20)].

The common name is the international non-proprietary name (INN) recommended by the World Health Organization, or, if one does not exist, the usual common name [DIR 2001/83/EC Art 1(21)].

The complete name of the medicinal product is the name of the medicinal product followed by the strength and pharmaceutical form.

Newly identified signal

In periodic benefit-risk evaluation reports, a signal first identified during the reporting interval, prompting further actions for evaluation (see Annex IV, ICH-E2C(R2) Guideline).

See also Signal

Non-interventional studies

A study fulfilling cumulatively the following requirements:

- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies include database research or review of records where all the

events of interest have already happened (e.g. case-control, cross-sectional and cohort studies). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met.

In this context, interviews, questionnaires and blood samples may be peformed as normal clinical practice.

Occupational exposure

An exposure to a medicinal product for human use as a result of one's occupation.

Ongoing clinical trial

Trial where enrolment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

See also Clinical trial, Completed clinical trial

Ongoing signal

In periodic benefit-risk evaluation reports, a signal that had been identified before the reporting interval and was still under evaluation at the data lock point (see Annex IV, ICH-E2C(R2) Guideline).

See also Signal, Data lock point

Overdose

Administration of a quantity of a medicinal product given per administration or per day which is above the maximum recommended dose according to the authorised product information. This also takes into account cumulative effects due to overdose.

Periodic safety update report (PSUR)

Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.

In the EU, periodic safety update reports should follow the format of a periodic benefit-risk evaluation report (PBRER) in accordance with the ICH-E2C(R2) Guideline (see Annex IV).

Pharmacovigilance

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see "The importance of pharmacovigilance", WHO[2]).

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

- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and

[2] World Health Organization (WHO). The importance of pharmacovigilance: safety monitoring of medicinal products. Genève: WHO; 2002.

- 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 the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [DIR 2001/83/EC Art 1(28d)].

In general, a pharmacovigilance system is a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

Pharmacovigilance system master file (PSMF)

A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products data [DIR 2001/83/EC Art 1(28e)].

See also Pharmacovigilance system

Post-authorisation safety study (PASS)

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product , or of measuring the effectiveness of risk management measures [DIR 2001/83/EC Art 1(15)].

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

See also Clinical trial, Non-interventional studies

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 safety concerns 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 (placebo or active substance, or unexposed 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 (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

See also Adverse event, Signal

Quality assurance

Activities focussing on providing confidence that quality requirements will be fulfilled (based on ISO 9000:2000 Standards[3]).

See also Quality requirements

Quality control

Activities focussing on fulfilling quality requirements while conducting given tasks or responsibilities.

See also Quality requirements

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.

See also Pharmacovigilance system, Quality system of a pharmacovigilance system

Quality requirements

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

See also Pharmacovigilance system, Quality system of a pharmacovigilance system

Quality system of a pharmacovigilance system

The organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system, including appropriate resource management, compliance management and record management [IM Art 10(2)].

The quality system is an integral part of the pharmacovigilance system [IM Art 12, Art 17(1)].

See also Pharmacovigilance system and Quality of a pharmacovigilance system

Reference safety information

Information referred to as the company core safety information (CCSI) (see Annex IV, ICH-E2C(R2) Guideline).

See also Company core safety information

Risk-benefit balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks [DIR 2001/83/EC Art 1(28a)] (i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health [DIR 2001/83/EC Art 1(28)]).

See also Risks related to use of a medicinal product

Risk management plan

A detailed description of the risk management system [DIR 2001/83/EC Art 1(28c)].

[3] Available from International Organization for Standardization (ISO).

To this end, it must identify or characterise the safety profile of the medicinal product(s) concerned; indicate how to characterise further the safety profile of the medicinal product(s) concerned; document measures to prevent minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation [IM Annex II.1.].

See also Risk management system, Risk minimisation activity

Risk management system

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions [DIR 2001/83/EC Art 1(28b)].

Risk minimisation activity; synonym: Risk minimisation measure

A public health 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 (see Annex IV, ICH-E2C(R2) Guideline).

These activities may consist of routine risk minimisation (e.g. product information) or additional risk minimisation activities (e.g. healthcare professional or patient communications/educational materials) (see Annex IV, ICH-E2C(R2) Guideline).

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 [DIR 2001/83/EC Art 1(28)].

Safety concern

An important identified risk, important potential risk or important missing information (see Annex IV, ICH-E2C(R2) Guideline).

See also Important identified risk and Important potential risk, Important missing information

Serious adverse reaction

Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)].

Life-threatening in this context 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 (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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 hospitalisation or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

See also Adverse reaction

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 [IM Art 23(1)].

For the purpose of the EudraVigilance database, only signals related to an adverse reaction shall be considered [IM Art 23(2)111].

See also Validated signal, Newly identified signal, Closed signal, Ongoing signal

Significant change in indication

A significant change in indication is a change of authorised indication(s) of a medicinal product where the new treatment target population differs materially from the one for which the medicinal product was previously authorised. This includes (but is not limited to): a new disease area, a new age group (e.g. paediatric indication) or a move from severe disease to a less severely affected population. It may also include a move from second line or other therapy or for an oncology product a change to the concomitant medication specified in the indication.

See also Target population (treatment)

Solicited sources of individual case safety reports

Organised data collection systems, which include clinical trials, registries, post-authorisation named-patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

For the purpose of safety reporting, solicited reports should be classified as individual case safety reports from studies and therefore should have an appropriate causality assessment by a healthcare professional or the marketing authorisation holder (see Annex IV, ICH-E2D).

See also Clinical trial, Post-authorisation safety study, Non-interventional study

Spontaneous report, synonym: Spontaneous notification

An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) 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 organised data collection scheme (see Annex IV, ICH-E2D).

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

Stimulated reporting can occur in certain situations, such as direct healthcare professional communication (DHPC), 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 (see Annex IV, ICH-E2D), provided the report meets the definition above.

Reporting made in the context of early post-marketing phase vigilance (EPPV), e.g. in Japan, is also considered stimulated reporting.

See also Adverse reaction

Target population (treatment); synonym: Treatment target population

The patients who might be treated by the medicinal product according to the indication(s) and contraindications in the authorised product information

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics [Dir 2001/83/EC Art 1(13)][4].

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. For products authorised nationally, the relevant SmPC is that approved by the competent authority in the Member State to whom the reaction is being reported. For centrally authorised products, the relevant SmPC is the SmPC authorised by the European Commission. During the time period between a CHMP opinion in favour of granting a marketing authorisation and the Commission decision granting the marketing authorisation, the relevant SmPC is the SmPC annexed to the CHMP opinion.

Validated signal

A signal where the signal validation process of evaluating the data supporting the detected signal has verified that the available documentation is strong enough to suggest a new potentially causal association, or a new aspect of a known association, and therefore justifies further assessment of the signal [based on IM Art 25(1)].

See also Signal

[4] Please note that for investigational medicinal products an unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the investigator's brochure for an unauthorised investigational product or the summary of product characteristics for an authorised product) [Dir 2001/20/EC Art 2(p)].