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Guideline on good pharmacovigilance practices (GVP)

Annex I - Definitions (Rev 5)

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*Note: Revision 5 includes the following:

- Deletion of the previous definition of Adverse event under Dir 2001/20/EC, as Reg (EU) No 536/2014 is now applicable (GVP A I Rev 4 had already included the update of the definitions of Adverse event as defined in Regulation (EU) No 536/2014 for the context of a clinical trial and as defined by ICH-E2D for the context of pharmacovigilance outside a clinical trial for the use of these definitions when Reg (EU) No 536/2014 becomes applicable);
- Deletion of Footnote 1 of GVP A I Rev 4 regarding the definition of Adverse reaction providing the definition under Dir 2001/20/EC for the context of a clinical trial, as Reg (EU) No 536/2014 is now applicable (GVP A I Rev 4 had already included a note that the Footnote would be deleted when Reg (EU) No 536/2014 becomes applicable; Reg (EU) No 536/2014 refers to DIR 2001/83/EC for the definition of Adverse reaction for the context of a clinical trial);
- Deletion of the note that the definition of Clinical study becomes applicable under Reg (EU) No 536/2014, as this Regulation is now applicable (GVP A I Rev 4 had already included this definition for use when Reg (EU) No 536/2014 becomes applicable);
- Deletion of the previous definition of Clinical trial under Dir 2001/20/EC, as Reg (EU) No 536/2014 is now applicable (GVP A I Rev 4 had already included the definition of Clinical trial as defined in Regulation (EU) No 536/2014 for use when Reg (EU) No 536/2014 becomes applicable);
- Addition of the definition of Disease registry in accordance with the CHMP Guideline on Registry-based Studies;
- Additions to the definition of Healthcare professional in accordance with GVP Module XVI Rev 3;

- Addition of the definition of Immunisation stress-related response (ISRR) which has become available since GVP A I Rev 4, to supplement the other definitions relating to adverse events following immunisation;
- Deletion of Footnote 11 of GVP A I Rev 4 regarding the definition of Individual case safety report providing the definition for the context of a clinical trial under Dir 2001/20/EC, as Reg (EU) No 536/2014 is now applicable (GVP A I Rev 4 had already included a note that the Footnote would be deleted when Reg (EU) No 536/2014 becomes applicable);
- Deletion of the previous definition of Investigational medicinal product under Dir 2001/20/EC, as Reg (EU) No 536/2014 is now applicable (GVP A I Rev 4 had already included the definition of Investigational medicinal product as defined in Regulation (EU) No 536/2014 for use when Reg (EU) No 536/2014 becomes applicable);
- Deletion of the note that the definition of Low-intervention clinical trial becomes applicable under Reg (EU) No 536/2014, as now this Regulation is applicable (GVP A I Rev 4 had already included this definition for use when Reg (EU) No 536/2014 becomes applicable);
- Update of the definition of Medical device in accordance with now applicable Reg (EU) 2017/745;
- Addition of explanatory notes to the definition of medication error in accordance with the EMA-PRAC Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors;
- Deletion of the definition of Non-interventional trial under Dir 2001/20/EC, as Reg (EU) No 536/2014 is now applicable (GVP A I Rev 4 had already included the definition of Non-interventional study under Reg (EU) No 536/2014 for use when Reg (EU) No 536/2014 becomes applicable) and addition of a reference to Annex I of the Questions & Answers Document - Regulation (EU) 536/2014, Volume 10 of the Rules Governing Medicinal Products in the EU;
- Deletion of the note that the definition of Normal clinical practice becomes applicable under Reg (EU) No 536/2014, as this Regulation is now applicable (GVP A I Rev 4 had already included this definition for use when Reg (EU) No 536/2014 becomes applicable);
- Addition of the definition of Patient in accordance with GVP Module XVI Rev 3;
- Addition of the definition of Primary data collection in accordance with the CHMP Guideline on Registry-based Studies;
- Deletion of the note that Footnote 14 of GVP A I Rev 4 regarding the definition of Reference safety information becomes applicable under Reg (EU) No 536/2014, as this Regulation is now applicable;
- Deletion of the previous definition of Registry and addition of the definition of Patient registry in accordance with the CHMP Guideline on Registry-based Studies;
- Addition of the definition of Registry-based study in accordance with the CHMP Guideline on Registry-based Studies;
- Addition of the definition of Registry database in accordance with the CHMP Guideline on Registry-based Studies;
- Addition of explanatory notes to the definition of Risk minimisation measure in accordance with GVP Module XVI Rev 3;
- Addition of the definition of Secondary use of data in accordance with the CHMP Guideline on Registry-based Studies;
- Addition of the definition of Target population (risk minimisation measure) in accordance with GVP Module XVI Rev 3;
- Deletion of the text in Footnote 17 of GVP A I Rev 4 regarding the definition of Unexpected adverse reaction which related to Dir 2001/20/EC, as Reg (EU) No 536/2014 is now applicable, and deletion of the note that the text relating to Reg (EU) No 536/2014 becomes applicable under Reg (EU) No 536/2014, as this Regulation is now applicable;
- Editorial improvements for a few definition entries and their alphabetical order.

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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)].

Active substance

Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis [DIR 2001/83/EC Art 1(3a)].

See also Substance

Advanced therapy medicinal product (ATMP)

A medicinal product for human use that is either a gene therapy medicinal product, a somatic cell therapy product or a tissue engineered products as defined in Regulation (EC) No 1394/2007 [Reg (EC) No 1394/2007 Art 1(1)].

Adverse event (AE)

In the context of a clinical trial: Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment [Reg (EU) No 536/2014 Art 2(2)(32)].

A subject means an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control [Reg (EU) No 536/2014 Art 2(2)(17)].

In the context of pharmacovigilance and outside a clinical trial: Any untoward medical occurrence in a patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment (based on ICH-E2D Guideline, see GVP Annex IV).

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 this medicinal product (see GVP Annex IV, ICH-E2D Guideline).

Adverse event following immunisation (AEFI)

See Vaccine pharmacovigilance, Vaccine product-related reaction, Vaccine quality defect-related reaction, Immunisation error-related reaction, Immunisation anxiety-related reaction, Immunisation stress-related response

Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect

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 GVP Annex IV, ICH-E2A Guideline). An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated by the by healthcare professional or consumer as primary source, it meets the definition of an adverse reaction (see GVP Annex IV, ICH-E2D). Therefore all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the

suspicions of the primary sources, unless the primary source specifically state that they believe the event to be unrelated or that a causal relationship can be excluded.

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)]. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors.

See also Adverse event, Serious adverse reaction, Unexpected adverse reaction, Off-label use, Overdose, Misuse of a medicinal product, Abuse of a medicinal product, Medication error, Occupational exposure to a medicinal product

Audit

A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled (see ISO 19011 (3.1)[1]).

Benchmarking, reviews of qualifications, risk assessment questionnaires, surveys or other activities in which evidence of fulfilment of pharmacovigilance requirements is not independently obtained and evaluated, would not be regarded as an audit.

Audit finding(s)

Results of the evaluation of the collected audit evidence against audit criteria (see ISO19011 (3.4)[2]).

Audit evidence is necessary to support the auditor's results of the evaluation, i.e. the auditor's opinion and report. It is cumulative in nature and is primarily obtained from audit procedures performed during the course of the audit.

See also Audit

Audit plan

Description of activities and arrangement for an individual audit (see ISO19011 (3.12)[3]).

See also Audit

Audit programme

Set of one or more audits planned for a specific timeframe and directed towards a specific purpose (see ISO 19011 (3.11)[4]).

See also Audit

Audit recommendation

Describes the course of action management might consider for rectifying conditions that have gone awry, and to mitigate weaknesses in systems of management control (see Sawyer LB et al, 2003[5]).

Audit recommendations should be positive and as specific as possible. They should also identify who is to act on them (see Sawyer LB et al, 2003[5]).

See also Audit

[1] International Organization for Standardization (ISO); www.iso.org
[2] International Organization for Standardization (ISO); www.iso.org
[3] International Organization for Standardization (ISO); www.iso.org
[4] International Organization for Standardization (ISO); www.iso.org
[5] Sawyer LB, Dittenhofer MA. Sawyer's Internal Auditing. 5th ed. Altamonte Springs, FL: The IIA Research Foundation; 2003.

Biological medicinal product

A medicinal product, the active substance of which is a biological substance [DIR 2001/83/EC, Annex 1, Part I, Section 3.2.1.1(b)].

A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control [DIR 2001/83/EC, Annex 1, Part I, Section 3.2.1.1(b)].

Biosimilar medicinal product

A biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal) product in the European Economic Area, and which has shown similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise (see EMA-CHMP Guideline on Similar Biological Medicinal Products Rev 1).

See also Biological medicinal product

Clinical study

Any investigation in relation to humans intended: (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products [Reg (EU) No 536/2014 Art 2(2)(1)].

See also Clinical trial, Non-interventional study

Clinical trial

A clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects [Reg (EU) No 536/2014 Art 2(2)(2)].

See also Clinical study, Low-intervention clinical trial, Investigational medicinal product, 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 GVP Annex IV, ICH-E2C(R2) Guideline).

A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk following evaluation (see GVP Annex IV, ICH-E2C(R2) Guideline).

This definition is also applicable to periodic safety update reports.

See also Signal, Refuted signal

Company core data sheet (CCDS)

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

See also Company core safety information

Company core safety information (CCSI)

For medicinal products, 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 (see GVP Annex IV, ICH-E2C(R2) Guideline).

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

See also Company core data sheet

Compassionate use of a medicinal product

Making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product (the medicinal product concerned must either be subject of an application for a central marketing authorisation or must be undergoing clinical trials) [REG (EC) No 726/2004 Art 83(2)].

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

Confirmed signal

For the signal management process in the EU, a validated signal entered in the European Pharmacovigilance Issues Tracking Tool (EPITT) that requires further analysis and prioritisation by the Pharmacovigilance Risk Assessment Committee (PRAC), according to the PRAC Rapporteur or (lead) Member State.

See also Validated signal, Signal management process, Signal confirmation by the PRAC Rapporteur or (lead) Member State, Signal analysis and prioritisation by the PRAC, Non-confirmed signal

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 of a patient (see GVP Annex IV, ICH-E2D Guideline) or carer.

See also Healthcare professional

Crisis

In the context of the European Union Regulatory Network Incident Management Plan for Medicines for Human Use, a crisis is defined as a situation where, after assessment of the associated risks, urgent and coordinated action within the EU regulatory network is required to manage and control the situation (see EMA-HMA European Union Regulatory Network Incident Management Plan for Medicines for Human Use).

See also Incident

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 GVP 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, 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).

Direct healthcare professional communication (DHPC)

A communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, 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.

Disease registry

A patient registry whose members are defined by a particular disease or disease-related patient characteristic regardless of exposure to any medicinal product, other treatment or particular health service.

See also Patient registry

Emerging safety issue

A safety issue considered by a marketing authorisation holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Examples include:

- major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
- major safety issues identified through the spontaneous reporting system or publications in the scientific literature, which may lead to considering a contraindication, a restriction of use of a medicinal product or its withdrawal from the market;
- major safety-related regulatory actions outside the EU, e.g. a restriction of use of a medicinal product or its suspension.

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)].

Excipient

Any constituent of a medicinal product other than the active substance and the packaging material [DIR 2001/83/EC Art 1(3b)].

Excipients include colouring matters, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances [DIR 2001/83/EC Annex I].

See also Active substance

Failure to vaccinate

An indicated vaccine was not administered appropriately for any reason (see CIOMS-WHO[6]).

For interpreting what is appropriate, consider the explanatory note for Immunisation error-related reaction.

See also Vaccination failure

Falsified medicinal product

Any medicinal product with a false representation of: (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients; (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or (c) its history, including the records and documents relating to the distribution channels used [DIR 2001/83/EC Art 1(33)].

[6] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights [DIR 2001/83/EC Art 1(33)].

Generic medicinal product

A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies [DIR 2001/83/EC Art 10(2)(b)].

Good pharmacovigilance practices (GVP) for the European Union (EU-GVP)

A set of guidelines for the conduct of pharmacovigilance in the European Union (EU), drawn up based on Article 108a(a) of Directive 2001/83/EC, by the European Medicines 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 the Member States.

Iceland, Liechtenstein and Norway have so far, through the Agreement of the European Economic Area (EEA), adopted the complete Union acquis (i.e. the legislation at EU level, guidelines and judgements) on medicinal products, and are consequently parties to the EU procedures. Where in the EU-GVP reference is made to Member States of the EU, this should be read to include Norway, Iceland and Liechtenstein[7].

Healthcare professional

In the context of reporting suspected adverse reactions: Medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners, or as otherwise specified by local regulations (see GVP Annex IV, ICH-E2D Guideline).

In the context of risk minimisation: A person providing professional healthcare[8] to individual patients, and also a healthcare professional representative or organisation (including learned societies and clinical guideline working groups) as target populations of risk minimisation measures.

The term healthcare professional does not include those who are qualified as a healthcare professional but work as employees of a marketing authorisation holder or a competent authority.

Herbal medicinal product

Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations [DIR 2001/83/EC Art 1(30)].

Herbal substances are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binominal system [DIR 2001/83/EC Art 1(31)].

[7] The only exemption from this is that legally binding acts from the EU (e.g. Commission Decisions) do not directly confer rights and obligations but have first to be transposed into legally binding acts in Norway, Iceland and Liechtenstein.
[8] More comprehensively, the following definition of health professional applies: a doctor of medicine, a nurse responsible for general care, a dental practitioner, a midwife or a pharmacist within the meaning of Directive 2005/36/EC, or another professional exercising activities in the healthcare sector which are restricted to a regulated profession as defined in Article 3(1)(a) of Directive 2005/36/EC, or a person considered to be a health professional according to the legislation of the Member State of treatment (see Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare)

Herbal preparations are preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates [DIR 2001/83/EC Art 1(32)].

Homeopathic medicinal product

Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles [DIR 2001/83/EC Art 1(5)].

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

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.

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)).

See also Risks related to use of a medicinal product, Important identified risk and Important potential risk, Missing information, Unexpected adverse reaction

Illegal purposes

See Misuse for illegal purposes

Immunisation

The process of making a person immune.

For the context of Considerations P.I, immunisation refers to the process of making a person immune to an infection.

See also Vaccination

Immunisation anxiety-related reaction

An adverse event following immunisation arising from anxiety about the immunisation (see CIOMS-WHO[9]).

In this definition immunisation means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[9]), which in the EU is preferably referred to as vaccination (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms immunisation and vaccination are used interchangeably[9]).

See also Vaccine pharmacovigilance, Vaccination, Immunisation stress-related response

Immunisation error-related reaction

An adverse event following immunisation that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable (see CIOMS-WHO[10]).

In this definition immunisation means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[10]), which in the EU is preferably referred to as vaccination (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms immunisation and vaccination are used interchangeably[10]).

Inappropriate refers to usage (handling, prescribing and administration) other than what is licensed and recommended in a given jurisdiction based on scientific evidence or expert recommendations (see CIOMS-WHO[10]).

See also Vaccine pharmacovigilance, Vaccination

Immunisation stress-related response (ISRR)

An adverse event following immunisation arising from stress about the process of immunisation (based on WHO[11]).

In contrast to immunisation anxiety-related reaction, ISRR covers the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom, anxiety (see WHO[11]).

As for other adverse events following immunisation (AEFI), symptoms may occur during or after immunisation; however, in contrast to other AEFI, the symptoms of an ISRR may also occur immediately before immunisation (see WHO[11]).

See also Immunisation anxiety-related reaction

Immunological medicinal product

Any medicinal product consisting of vaccines, toxins, serums or allergen products:

Vaccines, toxins and serums shall cover in particular agents used to produce active immunity (such as cholera vaccine, BCG, polio vaccine, smallpox vaccine), agents used to diagnose the state of immunity (including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin) and agents used to produce passive immunity (such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin).

[9] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.
[10] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.
[11] World Health Organization (WHO). Immunization stress-related response: a manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization. Geneva: WHO; 2019.

Allergen products shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent [DIR 2001/83/EC Art 1(4)].

BCG stands for Bacillus Calmette-Guérin vaccine and PPD for purified protein derivative.

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

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

Important potential risk

See Important identified risk and Important potential risk

Incident

A situation where an event occurs or new information arises, irrespective whether this is in the public domain or not, in relation to (an) authorised medicinal product(s) which could have a serious impact on public health (see European Union Regulatory Network Incident Management Plan for Medicines for Human Use).

The incident 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 incidents. 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 the definition of an incident (see European Union Regulatory Network Incident Management Plan for Medicines for Human Use).

In the context of this, the European Union Regulatory Network Incident Management Plan for Medicines for Human Use Incident Management Plan, an incident relates to (a) medicinal product(s) authorised in the EU, irrespective of their route of authorisation (see European Union Regulatory Network Incident Management Plan for Medicines for Human Use).

Individual case safety report (ICSR); synonym: Adverse (drug) reaction report, Suspected 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 [based on IR 520/2012 Art 25-29].

See also Minimum criteria for reporting

International birth date (IBD)

The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world (see GVP Annex IV, ICH-E2C(R2) Guideline).

If a marketing authorisation holder has no information on the actual IBD for a product, it should first refer to listings of birth dates that some regions develop and make publicly available. If the product is not included in any listing, it should propose to the regulatory authority a birth date that is based on the earliest known marketing authorisation of the substance and then obtain the regulatory authority's agreement (see GVP Annex IV, ICH-E2C(R2) Q&A).

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 Investigational medicinal product

Investigational medicinal product

A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial [Reg (EU) No 536/2014 Art 2(2)(5)].

See also Clinical trial

Labelling

Information on the immediate or outer packaging [DIR 2001/83/EC Art 1(25)].

Low-intervention clinical trial

A clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products, excluding placebos, are authorised; (b) according to the protocol of the clinical trial: (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned [Reg (EU) No 536/2014 Art 2(2)(3)].

See also Clinical trial

Medical device

Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability;
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state;

- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations;

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices: devices for the control or support of conception and products specifically intended for the cleaning, disinfection or sterilisation of devices (as referred to in Article 1(4) of Reg (EU) 2017/745 and of those referred to in the first paragraph of this point in Reg (EU) 2017/745) [Reg (EU) 2017/745 Art 2(1)].

Medication error

An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (see EMA-PRAC Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors, 23 October 2015).

A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures. Intentional overdose, off-label use, misuse and abuse should be clearly distinguished from medication errors (see EMA-PRAC Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors, 23 October 2015).

See also Off-label use, Overdose, Misuse of a medicinal product, Abuse of a medicinal product

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)].

Medicinal product derived from human blood or human plasma

Any medicinal product based on blood constituents which is prepared industrially by a public or private establishment, such as a medicinal product including, in particular, albumin, coagulating factor(s) and immunoglobulin(s) of human origin [DIR 2001/83/EC Art 1(10)].

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 (see GVP Annex IV, ICH-E2D Guideline).

In the case of expedited reporting, the individual case safety report shall include at least an identifiable reporter, an identifiable patient, one suspected adverse reaction and the medicinal product(s) concerned [IR 520/2012 Art 28(1)].

See also Individual case safety report

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 noted that there is an ICH definition for important missing information, which is: critical gaps in knowledge for specific safety issues or populations that use the marketed product (see GVP Annex IV, ICH-E2C(R2) Guideline). The change of the EU term, to name this concept "missing information" rather than "important missing information", is to be clear that in the EU a marketing authorisation cannot be granted if there are unacceptable gaps in knowledge, in accordance with Article 12 of REG (EC) No 726/2004 a marketing authorisation shall be refused if the quality, safety or efficacy are not properly or sufficiently demonstrated.

Misuse of a medicinal product

Situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

See also Misuse of a medicinal product for illegal purposes

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.

See also Misuse of a medicinal product

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.

Named patient use

Supply of a medicinal product which is excluded by a Member State from the provisions of Directive 2001/83/EC, in accordance with legislation in force and to fulfil special needs, in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility [based on DIR 2001/83/EC Art 5(1)].

Newly identified signal

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

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

This definition is also applicable to periodic safety update reports.

See also Signal, Closed signal

Non-confirmed signal

For the signal management process in the EU, a validated signal entered in the European Pharmacovigilance Issues Tracking Tool (EPITT) that does not require further analysis and prioritisation by the Pharmacovigilance Risk Assessment Committee (PRAC) at that point in time, according to the PRAC Rapporteur or (lead) Member State.

See also Validated signal, Signal management process, Signal confirmation by the PRAC Rapporteur or (lead) Member State, Signal analysis and prioritisation by the PRAC, Confirmed signal

Non-interventional study

A clinical study other than a clinical trial [Reg (EU) No 536/2014 Art 2(2)(4)].

Non-interventional studies do not fall in the scope of Regulation (EU) No 536/2014 [Reg (EU) No 536/2014 Art 1].

The table in Annex I of the Questions & Answers Document - Regulation (EU) 536/2014, Volume 10 of the Rules Governing Medicinal Products in the EU provides the difference between non-interventional studies and interventional trials.

See also Clinical study, Clinical trial, Normal clinical practice

Non-validated signal

A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted (see SCOPE Best Practice Guide on Signal Management[12]).

See also Signal validation, Validated signal

Normal clinical practice

The treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder [Reg (EU) No 536/2014 Art 2(2)(6)].

Occupational exposure to a medicinal product

For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.

It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as a different indication in terms of medical condition, a different group of patients (e.g. a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorisation in the country where the product is used.

[12] Strengthening Collaboration for Operating Pharmacovigilance in Europe Joint Action (SCOPE JA); www.scopejointaction.eu.

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 remains under evaluation at the data lock point (see GVP Annex IV, ICH-E2C(R2) Guideline).

This definition is also applicable to periodic safety update reports.

See also Signal, Data lock point

Overdose

Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information.

When applying this definition, clinical judgement should always be applied.

Package leaflet

A leaflet containing information for the user which accompanies the medicinal product [DIR 2001/83/EC Art 1(26)].

Patient

For the purpose of risk minimisation, an individual using or considering the use of a medicinal product (including (healthy) individuals using vaccines and other medicinal products not intended to treat or alleviate a disease) as well as the embryo/foetus/child who may be adversely affected by a medicinal product at conception, in utero or through breastfeeding, and an individual who may be adversely affected through occupational, accidental or illegal[13] exposure to a medicinal product, and also a parent, other carer and patient and consumer representative or organisation, as they may also be target populations of RMM.

Patient registry; synonym: Registry

Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure (see CHMP Guideline on Registry-based Studies, 21 October 2021).

Patients may be defined e.g. by a certain disease, pregnancy or breastfeeding status, or another condition such as a birth defect or a molecular or genomic feature (see CHMP Guideline on Registry-based Studies, 21 October 2021).

See also Disease registry

[13] See GVP Annex I for the definition of Misuse of a medicinal product for illegal purposes

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 described in GVP Module VII.

Pharmacovigilance

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see WHO[14]).

In line with this general definition, underlying objectives of pharmacovigilance in accordance with the applicable EU legislation for 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
- 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 [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 study

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

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

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

See also Adverse event, Signal

Primary data collection

Collection of data directly from patients, caregivers, healthcare professionals or other persons involved in patient care (see CHMP Guideline on Registry-based Studies).

Quality adherence

Carrying out tasks and responsibilities in accordance with quality requirements [IR 520/2012 Art 8(3)(b)].

See also Quality requirements

Quality assurance

See Quality control and assurance

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 [IR 520/2012 Art 8(3)(c)].

This applies for the purpose of fulfilling quality requirements.

See also Quality requirements

Quality improvements

Correcting and improving the structures and processes where necessary [IR 520/2012 Art 8(3)(d)].

This applies for the purpose of fulfilling quality requirements.

See also Quality requirements

Quality objectives

See 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 planning

Establishing structures and planning integrated and consistent processes [IR 520/2012 Art 8(3)(a)].

This applies for the purpose of fulfilling quality requirements.

See also Quality requirements

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 as well as appropriate resource management, compliance management and record management [IR 520/2012 Art 8(2)].

The quality system is part of the pharmacovigilance system.

See also Pharmacovigilance system, Quality of a pharmacovigilance system

Reference safety information

In periodic benefit-risk evaluation 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 authorisation holder and which the marketing authorisation holder requires to be listed in all countries where it markets the product, except when the local regulatory authority specifically requires a modification (see GVP Annex IV, ICH-E2C(R2) Guideline)[15].

It is a subset of information contained within the marketing authorisation holder's reference product information for the periodic benefit-risk evaluation report. Where the reference product information is the company core data sheet, the reference safety information is the company core safety information (see GVP Annex IV, ICH-E2C(R2) Guideline).

See also Company core data sheet, Company core safety information

Refuted signal

A validated signal which, following further assessment has been determined to be "false", i.e. a causal association cannot be established at that point in time.

[15] In the context of a clinical trial, if the investigator 's brochure is not a summary of product characteristics, it shall contain a clearly identifiable section called the 'Reference Safety Information' (RSI). … the RSI shall contain product information on the investigational medicinal product and on how to determine what adverse reactions are to be considered as expected adverse reactions, and on the frequency and nature of those adverse reactions [Reg (EU) No 536/2014 Annex 1.E.30]

It is noted that for the purpose of the periodic benefit-risk evaluation report (PBRER) ICH describes refuted signals as signals that, following evaluation, have been refuted as "false" signals based on medical judgment and a scientific evaluation of the currently available information (GVP Annex IV, ICH-E2C(R2) Guideline).

See also Validated signal, Signal assessment

Registry database; synonym: Register

Database derived from one or several registries (see CHMP Guideline on Registry-based Studies).

See also Patient registry

Registry-based study

Investigation of a research question using the data collection infrastructure or patient population of one or several patient registries (see CHMP Guideline on Registry-based Studies).

A registry-based study is either a clinical trial or a non-interventional study (see CHMP Guideline on Registry-based Studies).

A registry-based study may apply primary data collection in addition to secondary use of the existing data in the registry.

See also Patient registry, Clinical trial, Non-interventional study, Primary data collection, Secondary use of data

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 (RMP)

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

The risk management plan established by the marketing authorisation holder shall contain the following elements: (a) an identification or characterisation of the safety profile of the medicinal product(s) concerned; (b) an indication of how to characterise further the safety profile of the medicinal product(s) concerned; (c) a documentation of measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions; (d) a documentation of post-authorisation obligations that have been imposed as a condition of the marketing authorisation [IR 520/2012 Art 30(1)].

See also Risk management system, Risk minimisation measure

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 activities and interventions [DIR 2001/83/EC Art 1(28b)].

Risk minimisation measure (RMM); synonym: Risk minimisation activity

Interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicinal product, or to reduce their severity or impact on the patient should an adverse reaction occur.

Conceptually, a RMM consists of two components:

- RMM messages: the key information (i.e. not the full wording) about the risk and the actions intended to be taken by the healthcare professional or the patient for minimising the risk; and
- RMM tool: the tool by which the RMM messages are disseminated and adherence to the intended actions for risk minimisation is supported and/or controlled, belonging either to the category of routine RMM tools (summary of product characteristics, package leaflet, labelling of immediate and outer packaging, pack size, classification of the medicinal product) or additional RMM tools (e.g. educational/safety advice tools, Risk minimisation control tools).

RMM messages can be verbally explicit or non-verbal implicit (e.g. a restricted pack size as a RMM tool may imply e.g. the message that overdose is a specific risk to be avoided or that medical supervision of the treatment with this medicinal product is required; also a risk minimisation control programme, e.g. a traceability system or healthcare facility accreditation required for using a given medicinal product, carry implicit messages for the target audience); however, there will always be verbal messages at least in the product information and, if applicable, in further RMM materials.

For a specific medicinal product, a RMM material is the final individual RMM with its full wording in the local language(s) as approved by the competent authorities.

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 missing information.

It is noted that the ICH definition of safety concern is: an important identified risk, important potential risk or important missing information, i.e. includes the qualifier "important" in relation to missing information (see GVP Annex IV, ICH-E2C(R2) Guideline). The ICH-E2E Guideline (see GVP Annex IV) uses the terms safety issue and safety concern interchangeably with the same definition for safety concern as defined in the ICH-E2C(R2) Guideline.

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

Secondary use of data

Use of existing data for a different purpose than the one for which it was originally collected (see CHMP Guideline on Registry-based Studies).

Serious adverse reaction

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 GVP Annex IV, ICH-E2D Guideline).

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, 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 in the definition 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 GVP Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious 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 [IR 520/2012 Art 19(1)].

New aspects of a known association may include changes in the frequency, distribution (e.g. gender, age and country), duration, severity or outcome of the adverse reaction.

For the purpose of monitoring data in the EudraVigilance database, only signals related to an adverse reaction shall be considered [IR 520/2012 Art 19(1)].

For the purpose of Section 16.2 of the periodic benefit-risk evaluation report, signals relate to adverse effects (see GVP Annex IV, ICH-E2C(R2) Guideline).

See also Signal management process, Newly identified signal, Closed signal, Ongoing signal

Signal analysis and prioritisation by the PRAC

For the signal management process in the EU, the process by which the Pharmacovigilance Risk Assessment Committee (PRAC) determines whether a confirmed signal requires further assessment, and if required, to what timeframe and in which procedural framework, based on an initial analysis of the potential impact of the signal on patients' or public health and the risk-benefit balance of the concerned medicinal product(s).

See also Signal management process

Signal assessment

The process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally associated with the active substance or medicinal product or whether known risks have changed.

This process may include non-clinical and clinical data and should be as comprehensive as possible regarding the sources of information.

Within the signal management process in the EU, signal assessment by the Pharmacovigilance Risk Assessment Committee (PRAC), is, following PRAC's initial signal analysis and prioritisation, the process of evaluating all available data relevant to a signal to determine the need for any regulatory action.

See also Validated signal, Signal management process, Signal analysis and prioritisation by the PRAC

Signal confirmation by the PRAC Rapporteur or (lead) Member State

For the signal management process in the EU, the process of deciding whether or not a validated signal entered in the European Pharmacovigilance Issues Tracking Tool (EPITT) requires further analysis and prioritisation by the Pharmacovigilance Risk Assessment Committee (PRAC).

This process is not intended to be a full assessment of the signal. The fact that a signal is confirmed does not imply that a causal relationship has been established, but that the signal should be discussed at EU level and further investigated by the PRAC.

See also Validated signal, Confirmed signal, Non-confirmed signal, Signal management process

Signal detection

The process of looking for and/or identifying signals using data from any source (based on CIOMS VIII[16]).

Signal management process

A set of activities performed to determine whether, based on an examination of individual case safety reports, aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

The signal management process shall include the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action [IR 520/2012 Art 21(1)].

For explanations on active surveillance, see GVP Module VIII.App1.1.1..

See also Signal detection, Signal validation, Signal prioritisation, Individual case safety reports

Signal prioritisation

The process, continuously performed throughout signal management, which aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention and management without delay (based on SCOPE Best Practice Guide on Signal Management[17]).

See also Signal management process

Signal validation

Process of evaluating the data supporting the 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 [IR 520/2012 Art 21(1)].

This evaluation should take into account the strength of the evidence, the clinical relevance and the previous awareness of the association.

See also Signal detection, Validated signal, Non-validated signal

[16] Council for International Organizations of Medical Sciences (CIOMS). Practical aspects of signal detection in pharmacovigilance (report of CIOMS Working Group VIII). Genève: CIOMS; 2010.
[17] Strengthening Collaboration for Operating Pharmacovigilance in Europe Joint Action (SCOPE JA); www.scopejointaction.eu.

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 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 authorisation holder (see GVP 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 GVP 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 after a 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 GVP Annex IV, ICH-E2D), provided the report meets the definition above. Reporting can also be stimulated by invitation from patients' or consumers' organisations to their members, or a class lawsuit. Reporting made in the context of early post-marketing phase vigilance (EPPV), e.g. in Japan, is also considered stimulated reporting.

Stimulated reporting

See Spontaneous report

Strength of the medicinal product

The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form [DIR 2001/83/EC Art 1(22)].

See also Active substance

Substance

Any matter irrespective of origin which may be human (e.g. human blood and human blood products), animal (e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products), vegetable (e.g. micro-organisms, plants, part of plants, vegetable secretions, extracts), chemical (e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis) [DIR 2001/83/EC Art 1(3)].

Summary of product characteristics (SmPC)

Part of the marketing authorisation of a medicinal product setting out the agreed position of the product as distilled during the course of the assessment process which includes the information described in Article 11 of Directive 2001/83/EC. It is the basis of information for healthcare professionals on how to use the product safely and effectively. The package leaflet is drawn in

accordance with the summary of product characteristics (based on A Guideline on Summary of Product Characteristics, Volume 2C of the Rules Governing Medicinal Products in the EU Rev 2).

Target population (risk minimisation measure)

The group of individuals who are intended to either receive given risk minimisation measure (RMM) materials, be aware of the RMM messages and take the actions intended for risk minimisation, or to provide for systems in healthcare settings supporting that intended actions are taken.

When using this term, the definitions of patient and healthcare professional apply, and subgroups of these populations may be specified further, where applicable.

See also Patient, Healthcare professional

Target population (treatment); synonym: Treatment target population

The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information.

Target population (vaccine); synonym: Vaccine target population

Persons who might be vaccinated in accordance with the indication(s) and contraindications in the authorised product information and official recommendations for vaccinations.

Traditional herbal medicinal product

A herbal medicinal product that fulfils the conditions laid down in Article 16a(1) of Directive 2001/83/EC [DIR 2001/83/EC Art 1(29)], i.e.

(a) it has (an) indication(s) exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

(b) it is exclusively for administration in accordance with a specified strength and posology;

(c) it is an oral, external and/or inhalation preparation;

(d) the period of traditional use as laid down in Article 16c(1)(c) has elapsed;

(e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience [DIR 2001/83/EC Art 16a(1)].

Regarding (d), the product must have been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU (see DIR 2001/83/EC Art 16c(1)(c)).

See also Herbal medicinal product

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)][18].

[18] In the context of a clinical trial, an unexpected serious adverse reaction means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information [Reg (EU) No 536/2014 Art 2(2)(34)]

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 authorised 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.

See also Summary of product characteristics

Upper management

Group of persons in charge of the highest executive management of an organisation.

Membership of this group is determined by the governance structure of the organisation. While it is envisaged that the upper management usually is a group, the head of the organisation is the one person at the top of the organisation with ultimate responsibility for ensuring that the organisation complies with relevant legislation.

Vaccination

The administration of a vaccine with the aim to produce immune response.

See also Immunisation

Vaccination failure

Vaccination failure due to actual vaccine failure or failure to vaccinate (see CIOMS-WHO[19]).

Vaccination failure may be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity) (see CIOMS-WHO[19]).

See also Vaccine failure, Failure to vaccinate

Vaccine

See Immunological medicinal product

Vaccine failure

Confirmed or suspected vaccine failure.

Confirmed clinical vaccine failure

Occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunisation (see CIOMS-WHO[20]).

Suspected clinical vaccine failure

Occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, e.g. disease of unknown serotype in a fully vaccinated person (based on CIOMS-WHO[20]).

[19] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.
[20] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.

Confirmed immunological vaccine failure

Failure of the vaccinated person to develop the accepted marker of protective immune response after being fully and appropriately vaccinated, as demonstrated by having tested or examined the vaccinated person at an appropriate time interval after completion of immunisation (based on CIOMS-WHO[20].

Suspected immunological vaccine failure

Failure of the vaccinated person to develop the accepted marker of protective immune response after being fully and appropriately vaccinated, but with the testing or examination of the vaccinated person done at an inappropriate time interval after completion of immunisation (based on CIOMS-WHO[20]).

For interpreting what means appropriately vaccinated, consider the explanatory note for Immunisation error-related reaction.

See also Vaccination failure

Vaccine pharmacovigilance

The science and activities relating to the detection, assessment, understanding and communication of adverse events following immunisation and other vaccine- or immunisation-related issues, and to the prevention of untoward effects of the vaccine or immunisation (see CIOMS-WHO[21]).

In this definition, immunisation means the usage of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[21]), which in the EU is preferably referred to as vaccination (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms immunisation and vaccination are used interchangeably[21]). Usage includes all processes that occur after a vaccine product has left the manufacturing/packaging site, i.e. handling, prescribing and administration of the vaccine (see CIOMS-WHO[21]).

An adverse event following immunisation (AEFI) is any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. While this AEFI definition is compatible with the definition of adverse event applied in the EU, the AEFI definition is not needed to describe pharmacovigilance for vaccines in the EU. However, EU guidance on pharmacovigilance for vaccines makes use of the terminology suggested by CIOMS-WHO[21] regarding possible causes of adverse events, turning them into suspected adverse reactions. A coincidental event is an AEFI that is caused by something other than the vaccine product, immunisation error or immunisation anxiety (see CIOMS-WHO[21]).

See also Adverse event, Vaccine product-related reaction, Vaccine quality defect-related reaction, Immunisation error-related reaction, Immunisation anxiety-related reaction, Immunisation stress-related response, Vaccination

Vaccine product-related reaction

An adverse event following immunisation that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product (see CIOMS-WHO[22]).

In this definition immunisation means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[22]), which in the EU is preferably referred to as vaccination (in

[21] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.
[22] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.

the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms immunisation and vaccination are used interchangeably[22]).

See also Vaccine pharmacovigilance

Vaccine quality defect-related reaction

An adverse event following immunisation that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer (see CIOMS-WHO[23]).

In this definition immunisation means the usage (handling, prescribing and administration) of a vaccine for the purpose of immunising individuals (see CIOMS-WHO[23]), which in the EU is preferably referred to as vaccination (in the report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance the terms immunisation and vaccination are used interchangeably[23]).

For the purpose of this definition, a vaccine quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications (see CIOMS-WHO[23]).

See also Vaccine pharmacovigilance

Valid individual case safety report

See Individual case safety report

Validated signal

A signal for which the signal validation process 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.

See also Signal validation, Non-validated signal

[23] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.