PHARMACOVIGILANCE GLOSSARY

Note: This glossary has been prepared for informative purpose. Please refer to the currently valid guidance as applicable (GVP Annex I Rev. 3, GVP module V Rev. 2, and GVP module VI Rev. 2; further guidance is quoted in the glossary).

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Section 1

Terms used for Side Effects		
Term	**Definition**	**Relevance**
Side effect	Unintended effect occurring at normal dose related to the pharmacological properties.	Lay-man‘s term to describe an adverse event
AE	**Adverse Event** **Any** untoward medical occurrence in a patient or clinical trial subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. 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.	Standard definition of an AE. Important thing to remember here is that it is associated with the use of the product; however, it is not necessarily causally related to the medicinal product. E.g.: a patient took a medicine and fell of a horse accidentally and broke his leg. Breaking his leg would be considered an AE even though it is not related to the medicine.
SAE	**Serious Adverse Event** An adverse event 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.	In addition to the specific seriousness criteria listed in the definition, medical judgment should be used to assess an AE as serious due to its medical importance. The EudraVigilance Expert Working Group has co-ordinated the development of an important medical event (IME) terms list based on the Medical Dictionary for Regulatory Activities (MedDRA). This IME list aims to facilitate the seriousness classification of suspected adverse reactions. The seriousness criterion ‘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.

ADR	**Adverse Drug Reaction** A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.	Note how ADR differs from AE (above). When we use the word "reaction", we assign at least a reasonable possibility of a causal relationship, whereas the term AE does not imply a causal relationship.
SAR	**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. "Reaction" means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.	Same subtle difference as AE and ADR described above. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
Unexpected Adverse Reaction	An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information.	Any event that is not expected, in accordance with the label (USPI in the US and SmPC in Europe), is considered an unexpected event. Importantly, if an event is listed in the label, but occurs at a higher severity or with a worse outcome than the event listed in the label, is also considered unexpected. 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).
SUSAR	**Suspected Unexpected Serious Adverse Reaction** A SUSAR is a serious ADR whose nature or severity is unexpected based on the applicable product information.	The same considerations as above apply; however, this term only refers to serious events.

Abuse	Persistent or sporadic, intentional excessive use of medicinal product, which is accompanied by harmful physical or psychological effects.	Although being a condition of use outside the marketing authorisation, abuse can lead to ADRs.
Medication error	A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures.	This term is related to the way a drug is taken or administered, rather than to the effect it causes. A drug could be wrongly prescribed by a doctor or pharmacist, wrongly dispensed by a nurse or caregiver, or administered incorrectly by a caregiver or patient himself/herself. Although being a condition of use outside the marketing authorisation, medication errors can lead to ADRs. The EMA guidance "Good practice guide on recording, coding, reporting and assessment of medication errors" (EMA/762563/2014, 23 October 2015) points out that medication errors may occur at all stages of the drug treatment process (e.g. prescribing, storage, dispensing, preparation, administration).
Misuse	Situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.	Although being a condition of use outside the marketing authorisation, misuse can lead to ADRs.

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.	When drugs are approved by regulators, they get specific approval to use it for a certain indication or population or dose, only. However, sometimes it is noticed that the drug is intentionally prescribed for a medical purpose it is not explicitly indicated for. Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as: • Medicine used for disease or medical condition that it is not approved to treat • Medicine administration through different route or method of administration • Medicine used with different dose (posology) • Medicine used in different group of patients (population) Although being a condition of use outside the marketing authorisation, off-label use can lead to ADRs. The element of 'intention' differentiates some of the off-label uses from the medication error at prescriber level. For example, if the doctor intentionally prescribes/administers a drug by unauthorised route of administration, this would be called off-label use. However, if the doctor unintentionally (i.e. by mistake/error) prescribes/administers a drug by unauthorised route of administration, this would be called a medication error.

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. Clinical judgement should always be applied.	As described above there is a maximum permissible dose for every medicinal product. When it is administered above the maximum recommended dose it is considered as an overdose. Although being a condition of use outside the marketing authorisation, overdose can lead to ADRs.

Section 2

Drug Safety Concepts		
Term	**Definition**	**Relevance**
Causal relationship	According to the WHO, the causal relationship between an adverse event and a suspected drug can be: • certain • probable/likely • possible • unlikely • conditional/unclassified • unassessable/unclassifiable. Causal assessment is determined based on temporal relationship, alternative explanations, and (if possible) dechallenge and rechallenge.	To determine the causal relationship (i.e., to assess whether the drug caused the AE/ADR), several medical aspects are evaluated. Elements to assess the causal relationship are e.g. drug's half-life, pathological mechanisms, temporal relationship of event to drug administration, dechallenge and rechallenge, concomitant diseases and/or concomitant use of other medicines, previous experience with the drug, and possible alternative explanations for the event.
Critical terms	The WHO marked some terms as 'Critical Terms'. These terms either refer to or might be indicative of serious disease states, and warrant special attention, because of their possible association with the risk of serious illness that may lead to more decisive action than reports on other terms.	The WHO list of Critical Terms may serve as a basis for medical judgment of AEs, i.e. to assess whether AEs should be considered serious due to their medical importance.
Important medical event (IME)	The EudraVigilance Expert Working Group has co-ordinated the development of an important medical event (IME) terms list based on the Medical Dictionary for Regulatory Activities (MedDRA). This IME list aims to facilitate the classification of suspected adverse reactions, the analysis of aggregated data and the assessment of ICSRs in the framework of the day-to-day pharmacovigilance activities. The IME list is intended for guidance purposes only and is available on the EMA website to stakeholders who wish to use it for their pharmacovigilance activities. It is regularly updated in line with the latest version of MedDRA.	IME list can be used to facilitate seriousness assessment of AEs.

Designated medical event (DME)	DMEs are serious and rare medical events that are often causally associated with drugs across multiple pharmacological/therapeutic classes.	DMEs are serious, rare and often causally associated with drugs. Therefore, even small number of reports of such event can trigger a signal and require special attention. Organisation may maintain such list, to prioritise cases of such event for safety review. EMA maintains a list MedDRA Preferred Terms that identifies DMEs. The content of the EMA DME list is not definitive and may change as EMA gathers further experience with its use.
Dechallenge	The clinical decision to withdraw or discontinue a drug to monitor the effect on an adverse event.	Dechallenge (and rechallenge) play an important role in ascertaining a causal relationship. Dechallenge means that a drug that is suspected of causing the event is withdrawn. A dechallenge is positive when after removal of the drug the adverse event subsides or disappears. A dechallenge is negative when the event persists even after removal of the drug i.e. a causal relationship is unlikely.
Rechallenge	The point at which a drug is given again to a patient after its previous withdrawal.	In the instance you have a positive dechallenge (AE subsides or disappears after you remove the drug), reintroducing the drug represents a rechallenge. A positive rechallenge (i.e., the AE reappears when treatment is restarted), strongly suggests a causal relationship.
Efficacy	The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical and in clinical research conditions.	
Seriousness vs. severity	The term ‘severe’ must not be confused with ‘serious’. In the English language, ‘severe’ is used to describe the intensity (severity) of a specific event (mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) is based on patient/event outcome or action criteria, and serves as a guide for defining regulatory reporting obligations.	Understanding the difference between seriousness and severity is critical to correctly reporting and evaluating AEs.

Temporal relationship	Temporal relationship is considered positive if the event occurred during the use of the drug and/or within a plausible range based on the half-life of the drug. Categories for temporal relationship are: • positive • suggestive • compatible • weak • negative The temporal relationship is assessed based on drug kinetics, toxicity mechanisms, involved organ, and the physiopathology of the event.	Is the timeframe between treatment and occurrence of the AE compatible with the drug's half-life?.E.g.: an allergic reaction usually occurs shortly after being exposed to that substance. This indicates a positive temporal relationship. On the other hand, if an event occurs days after exposure to a drug with a short half life, there is a very weak or a negative temporal relationship.

Section 3

Risk Terminology		
Term	**Definition**	**Relevance**
Identified risk	Definition according to GVP Annex I (Rev 3): An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Explanatory wording provided in GVP module V (Rev 2): Undesirable clinical outcomes for which there is sufficient scientific evidence that they are caused by the medicinal product.	Identified risks can arise e.g. from signal evaluation and are described and classified (i.e., important or not important) in the PSUR / PBRER. Identified risks have usually been observed in clinical trials or in clinical practice and are described in the SmPC. The causal relationship is already **documented**. Note: the definition provided in GVP Annex I remains valid. GVP module V Rev. 2 provides clarifications on how to apply the definition.
Potential risk	Definition according to GVP Annex I (Rev 3): 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. Explanatory wording provided in GVP module V (Rev 2): Undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal.	Potential risks have not necessarily been observed in clinical trials or in the clinical practice; however, pre-clinical or clinical considerations point to a **possible** causal association to the medicinal product. Potential risks can be identified e.g. from signal evaluation and are described and classified (i.e., important or not important) in the PSUR / PBRER. Note: the definition provided in GVP Annex I remains valid. GVP module V Rev. 2 provides clarifications on how to apply the definition.

Important risk	Definition according to GVP Annex I (Rev 3): 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. Explanatory wording provided in GVP module V (Rev 2): The RMP should focus on the important identified risks that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant: • Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk); • Risk minimisation activities: product information advising on specific clinical actions to be taken to minimise the risk, or additional risk minimisation activities. The important potential risks to be included in the RMP are those important potential risks that, when further characterised and if confirmed, would have an impact on the risk-benefit balance of the medicinal product.	Important risks are identified, characterised, and monitored in the DSUR; the RMP, and in the PSUR / PBRER. To define the important risks of a medicinal product, the overall knowledge on the safety profile of a drug is evaluated (e.g., mechanisms of action, epidemiology of the populations exposed, risk factors or risk groups, pre-clinical, clinical and, if available, post-marketing experience).

Missing information	Definition according to GVP Annex I (Rev 3): (Critical) gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant. Explanatory wording provided in GVP module V (Rev 2): Gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far.	Missing information is identified, characterised, and monitored in the RMP and the PSUR / PBRER. Typical examples of missing information are the use of a medicinal product in pregnant and lactating women or in the paediatric population, if there are not adequate clinical studies in these patients. The decision on whether the lack of safety information in a specific population is critical (=missing information) is based on clinical considerations.
Risks related to the 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	The risks related to the use of a medicinal product are investigated, identified, characterised, monitored, and minimised throughout the life-cycle of a drug. Risks can be identified e.g. from signal evaluation and are described and classified (i.e., important or not important; identified or potential) in the PSUR / PBRER. New important risks trigger an RMP update.
Risk-benefit balance	An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health	The risk-benefit balance of a medicinal product is continuously monitored through pharmacovigilance activities and periodical safety reports, such as DSURs and PBRERs
Safety concern	An important identified risk, important potential risk or missing information	The safety concerns of a medicinal product are identified, characterised, and monitored in the DSUR; the RMP, and in the PSUR / PBRER.
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 further investigation	Signals are continuously monitored and evaluated by the company. New signals which emerge, remain ongoing, or are closed during the reporting period are presented in the PSUR / PBRER

Section 4

General Pharmacovigilance Terms		
Term	**Definition**	**Relevance**
CCDS	**Company Core Data Sheet** The CCDS is a document that reflects the full company's knowledge and data evaluation for a medicinal product	The safety information contained in the CCDS is referred to as the CCSI (see next definition).
CCSI	**Company Core Safety Information** The CCSI is the safety information contained in the CCDS	The CCSI is generally used in all countries where the company markets the medicinal product and is the reference information used to determine listed and unlisted events for the purpose of periodic reporting for marketed products
DIBD	**Developmental International Birth Date** Date of approval of the first authorization for conducting an interventional clinical trial in any country	Determines the start of regulatory requirement. The first data lock point for the DSUR is the first anniversary of the DIBD.
DLP	**Data Lock Point** Data lock for data analyses	The DLP represents the cut-off date for data and analyses presented in a document. It is based on the DIBD for the DSURs and on the IBD for PSURs / PBRERs. For RMPs, the DLP can be chosen based e.g. on the cut-off date of the clinical and/or post-marketing data to be included
DSUR	**Development Safety Update Report** Comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period **related to a drug under investigation**, whether or not it is marketed	A DSUR provides information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug

IB	**Investigator´s Brochure** The IB is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.	The IB provides the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. For investigational products not yet authorised, the IB serves as the CCDS
IBD	**International Birth Date** The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world	Determines the start of regulatory requirement and the first data lock point for the PSUR / PBRER
Periodic Safety Update Report (PSUR) / Periodic Benefit-Risk Evaluation Report (PBRER)	Pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points **during the post-authorisation phase**	A PSUR / PBRER provides an analysis of the risk-benefit profile of a medicinal product based on the safety, efficacy and effectiveness information that becomes available in the reporting period and in the context of the cumulative experience with the medicinal product since DIBD. A PSUR / PBRER also evaluates the effectiveness of the risk minimisation measures described in the RMP.

Pharmacovigilance	A set of activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem	Pharmacovigilance covers the entire life-cycle of a medicinal product Underlying objectives of 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 • 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.
Regulatory authority	The legal authority that is responsible for regulating all matters relating to drugs and medicinal products (e.g.: EMA, FDA, MHRA)	The activities of regulatory authorities protect, promote, and maintain the health and safety of the public by ensuring proper standards for the profession of medicine
RMP	**Risk Management Plan** A detailed description of the risk management system.	The RMP is a dynamic, stand-alone document that should be updated throughout the life-cycle of the medicinal product to reflect the increasing knowledge on risks and benefits and the post-marketing experience with the product.
RMS	**Risk management system** A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions.	The RMS covers the entire life-cycle of a medicinal product.

SmPC	**Summary of Product Characteristics** The SmPC is a legal document approved as part of the marketing authorisation of a medicinal product in the European Union.	The SmPC is the basis of information for the healthcare professional on how to use the medicine. Its information is updated throughout the life-cycle of the product as new data emerge. The SmPC is the reference information used to determine expected or unexpected status of events for marketed products for the purpose of expedited reporting.