

WHO-Definitions

- Pharmacovigilance
- Side Effect - Adverse Reaction
 - Comments
- Serious Adverse Event or Reaction
- Causality Assessment of Suspected Adverse Reactions
 - Using the WHO-UMC system for standardised case causality assessment (including downloadable pdf)
- Frequency of Adverse Drug Reactions
- Concepts in Critical Terms
- WHO Aide Memoire for Pharmacovigilance (English, French, Russian)
- The Erice Declaration - Effective Communications in Pharmacovigilance

[Top of page]

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

Source: The Importance of Pharmacovigilance, WHO 2002

[Top of page]

Side Effect - Adverse Reaction

- as adopted by National Centres participating in the WHO International Drug Monitoring Programme, September 1991

The definitions below have been agreed by Programme members after extensive consultation. In the first place member countries were asked what terms they used in their work and to give working definitions. These were then collated and the compilation was used to create a composite definition of each term. These were subsequently circulated until agreement was reached about each definition.

Not all terms are used by every member country, particularly the causality terms, and the reader is encouraged to note the comments on the hierarchical use of causality terms.

Term / Definition	Comment
ADVERSE REACTION WHO Technical Report No 498 (1972); 'A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.'	<i>This basic definition includes all doses prescribed clinically, but is intended to exclude accidental or deliberate overdose. The subclassification of 'unexpected' was included to facilitate understanding of the type of adverse reaction which are most important to report to drug monitoring agencies.</i>

<p>UNEXPECTED ADVERSE REACTION</p> <p>An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.</p>	
<p>ADVERSE EVENT/ ADVERSE EXPERIENCE</p> <p>Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.</p>	<p><i>This is a more recent term which some use interchangeably with 'adverse reaction', but, as indicated, it is better reserved for clinical phenomena occurring during drug treatment where the possibility of a causal connection has not been considered.</i></p>
<p>SIDE EFFECT</p> <p>Any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug.</p>	<p><i>This is an old term and is broad enough to include both positive and negative effects of a drug apart from its main properties or indications. Some use the term as synonymous with 'adverse reaction', but the proposed definition will improve clarity of use of this term.</i></p>
<p>SIGNAL</p> <p>Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.</p>	<p><i>This describes the first alert of a problem with a drug. By its nature a signal cannot be regarded as definitive but indicates the need for further enquiry or action. On the other hand it is prudent to avoid a multiplicity of signals based on single case reports since follow up of all such would be impractical and time consuming. The definition allows for some flexibility in approach to a signal based on the characteristics of individual problems. Some would like a 'signal' to include new information on positive drug effects, but this is outside the scope of a drug safety Programme.</i></p>

Reference: Delamothe T. Reporting adverse drug reactions. *British Medical Journal*, 1992, 304:465.

[Top of page]

Serious Adverse Event or Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is life-threatening

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', the following note of clarification is provided:

The term 'severe' is not synonymous with serious. In the English language, 'severe' is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe): the event itself, however, may

be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on patient/event outcome or action criteria serves as guide for defining regulatory reporting obligations.

(In order to facilitate the distinction between these terms in different languages, recommended translations are given below.)

English	Serious	Severe
Czech	Závažný	Tezký
Croatian	Ozbiljno	Tesko
Danish	Alvorlig	Svaer
Dutch	Ernstig	Zwaar (or Ernstig ²)
French	Grave	Sévère
German	Schwerwiegend	Schwer
Greek	Varys	Sovaros
Italian	Serio	Severo (or Grave)
Japanese	Juhtoku	Juhshoh
Portuguese	Grave	Severo (or Intenso)
Spanish	Grave	Severo (or Intenso)
Swedish	Allvarlig	Svår (or Intensiv)
Turkish	Ciddi	Siddetli

[Top of page]

Causality Assessment of Suspected Adverse Reactions

Term	Description	Comments
CERTAIN	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	It is recognized that this stringent definition will lead to very few reports meeting the criteria, but this is useful because of the special value of such reports. It is considered that time relationships between drug administration and the onset and course of the adverse event are important in causality analysis. So also is the consideration of confounding features, but due weight must be placed on the known pharmacological and other characteristics of the drug product being considered. Sometimes the clinical phenomena described will also be sufficiently specific to allow a confident causality assessment in the absence of confounding features and with appropriate time relationships, e.g. penicillin anaphylaxis.
PROBABLE/ LIKELY	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).	This definition has less stringent wording than for 'certain' and does not necessitate prior knowledge of drug characteristics or clinical adverse reaction phenomena. As stated no rechallenge information is needed,

	Rechallenge information is not required to fulfil this definition.	but confounding drug administration underlying disease must be absent.
POSSIBLE	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	This is the definition to be used when drug causality is one of other possible causes for the described clinical event.
UNLIKELY	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	This definition is intended to be used when the exclusion of drug causality of a clinical event seems most plausible.
CONDITIONAL/ UNCLASSIFIED	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.	
UNASSESSIBLE/ UNCLASSIFIABLE	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	

Causality Assessment - comments

Various causality terms are in use but the above are used most widely. Some people, however, do not use all the terms. For instance, many do not believe that a 'certain' classification is possible for a single report and others make no distinction between 'probable' and 'possible'. These definitions are however# acceptable to Programme members who do use the terms. Where only 'possible' or 'unlikely' are used to describe reactions it must be understood that 'possible' include those reactions which are called by others 'probable' and 'certain', as well as 'possible'.

Whilst 'conditional/unclassified' and 'unassessible/unclassifiable' are not causality terms, they describe the status of adverse reaction reports and therefore allow for practical communication about ADR issues.

[\[Top of page\]](#)

WHO-UMC causality assessment system

For a fuller explanation of the use of the [WHO-UMC system for standardised case causality assessment](#), please download this Adobe Acrobat document (125KB). If you have any comments on causality or relationships in pharmacovigilance, please contact [Dr Ronald Meyboom](#).

[\[Top of page\]](#)

Frequency of adverse drug reactions

Guidelines for Preparing Core Clinical Safety Information on Drugs

Report from CIOMS Working Group III, Geneva 1995

Whenever possible, an estimate of frequency should be provided, expressed in standard category of frequency.

It is always difficult to estimate incidence on the basis of spontaneous reports, owing to the uncertainty inherent in estimating the denominator and degree of under-reporting. However, the Working Group felt that, whenever possible, an estimate of frequency should be provided and in a standard form. The following standard categories of frequency are recommended:

<i>Very common*</i>	$\geq 1/10$	($\geq 10\%$)
<i>Common (frequent)</i>	$\geq 1/100$ and $< 1/10$	($\geq 1\%$ and $< 10\%$)
<i>Uncommon (infrequent)</i>	$\geq 1/1,000$ and $< 1/100$	($\geq 0.1\%$ and $< 1\%$)
<i>Rare</i>	$\geq 1/10,000$ and $< 1,000$	($\geq 0.01\%$ and $< 0.1\%$)
<i>Very rare*</i>	$< 1/10,000$	(< 0.01%)

* Optional categories

Precise rates will inevitably be based on studies and limited to the more common reactions. For reactions that are fewer than 'common', estimates of frequency will inevitably be based on spontaneous reports or on very large post-marketing studies or other special studies, and the numbers will be less precise; therefore, the source of the estimates (spontaneous or clinical) should be indicated. Stating the absolute numbers of cases reported may be misleading since they inevitably will become outdated.

Reference: *Guidelines for Preparing Core Clinical Safety Information on Drugs - Report of CIOMS Working Group III. Geneva, WHO, 1995. (Chapter 5, Good Safety Information Practices)*

[\[Top of page\]](#)

Concepts in Critical Terms

Some of the terms in WHO-ART are marked as 'Critical Terms'.

The word 'critical' is taken to mean 'relating to a crisis' or 'decisive' or 'crucial'. Thus the terms which are marked as Critical Terms do not necessarily refer to serious conditions in themselves, but are terms which may be part of or lead to a serious syndrome.

The logic that underpins the choice of terms is:

- that they should have been reported within the WHO Programme as adverse reaction terms
- that the terms either refer to or might be indicative of a serious disease state. A serious disease is one that may be fatal, life-threatening, involved or prolonged inpatient hospitalisation, or resulting in persistent or significant disability or incapacity
- that reports including critical terms warrant special attention, because of their possible association with serious disease states and may lead to more decisive action than reports on

other terms

The frequency with which the terms has been used has not been taken into consideration in selecting Critical Terms.

[\[Top of page\]](#)

WHO Aide Memoire for Pharmacovigilance

The WHO has produced a short 'Aide Memoire' for Pharmacovigilance. It is available here in Adobe pdf format in English, French and Russian languages. Either left click on the language or right click and 'Save target as...'

 ENGLISH (150KB)

 FRENCH (130KB)

 RUSSIAN (300KB)

[\[Top of page\]](#)

Effective Communications in Pharmacovigilance - The Erice Declaration

The following declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance, Erice, Sicily, 24-27 September 1997. It was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organisations.

Preamble:

Monitoring, evaluating and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties - consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organisations - working together. High scientific, ethical and professional standards and a moral code should govern this activity. The inherent uncertainty of the risks and benefits of drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be informed by scientific and clinical considerations and should take into account social realities and circumstances.

Declaration:

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

The following statements set forth the basic requirements for this to happen, and were agreed upon by all participants from 34 countries at Erice:

1. Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions

should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.

2. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.

3. All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal must be recognised and overcome.

4. Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.

5. A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated.

These ideals are achievable and the participants at the conference commit themselves accordingly. Details of what might be done to give effect to this declaration have been considered at the conference and form the substance of the conference report.

Erice, September 27 1997

The Conference was organised by:

the Uppsala Monitoring Centre; the Clinical Pharmacology Unit, Institute of Pharmacology of Verona University; the Ettore Majorana Centre for Scientific Culture, International School of Pharmacology; the World Health Organisation and supported by EQUUS Communications, London

The full report from the conference is available from *the* UMC. Please contact the [Sales Department](#) at *the* UMC to order your own copy of the Erice Report.
