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The Need for Definitions in Pharmacovigilance

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All human communication depends on our ability to convey and correctly interpret messages; the language is the means by which a message is transmitted. Language can be expressed by the use of words, either oral or written, but also by gestures and other body signals, sounds, signs or marks.

The language expressions, for instance the words we use, are not intrinsically meaningful; they denote a particular concept, in a given context. For a message to make sense, the concepts and the terms used must be understood, and understood in the same way, by everyone involved in the communication. Within a given setting, this understanding might be implicit, without explanation or written definitions.

However, for communications between and outside of confined areas of mutual understanding, there is always a risk of misinterpretations, unless agreed-on definitions of concepts are established and used actively. A definition should be easy to grasp and provide a concise and unambiguous description of a concept. Accurate and clear definitions facilitate interpretation between different professional areas and groups and translations, which is essential in an international setting.

In its global normative function, the WHO has generally been very much concerned with definitions that are understandable by a variety of cultures and can be translated into the main language groups. Over the years, the definitions of some fundamental pharmacovigilance terms have been agreed within all the countries belonging to the WHO Programme for International Drug Monitoring.[1]

The term 'pharmacovigilance' was first introduced in France, but has in the last decade become probably the most commonly used term internationally for "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems". This definition was published by the WHO in 2002,[2] and has since been adopted by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The Uppsala Monitoring Centre (UMC) is responsible for the scientific and technical operations of the WHO Programme for International Drug Monitoring (which, somewhat ironically, has retained its original name). The UMC has for a long time been concerned with the need for better communication between all stakeholders in international pharmacovigilance. A series of meetings to address the issues involved were held in the late 1990s, with participation of a wide range of experts representing different disciplines and interest groups, and sponsored by WHO and the Council for International Organizations of Medical Sciences (CIOMS).

Definitions of key terms in pharmacovigilance communications were discussed and agreed in this forum. The result of the deliberations, a booklet titled *Dialogue in Pharmacovigilance – more effective communications*, was published by the UMC in 2002.[3] With the exception of some minor updates, the definitions in table I are the same as those included in this publication.

Table I. Definitions used in pharmacovigilance. When a defined term is referred to elsewhere in this table, it is written in *italics*. 'Includes' does not imply an exhaustive listing. 'Synonym' means that the term given as a synonym can be used interchangeably with the preferred, defined term

Term	Definition
Absolute risk	*Risk* in a population of exposed persons (c.f. *Reference risk*) Note: absolute risk can be measured over time (see *Incidence*) or at a given time (see *Prevalence*) See also *Attributable risk* and *Relative risk*
Adverse event	Any untoward medical occurrence that may present during treatment with a *Medicinal product* but which does not necessarily have a causal relationship with this treatment (WHO, 1991) Synonym: adverse experience
Adverse reaction	Response that is noxious and unintended, and that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1991) Synonyms: adverse drug reaction (ADR), suspected adverse (drug) reaction Note: an adverse reaction, contrary to an *Adverse event*, is characterised by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged possible by the reporting or a reviewing *Health professional*
Attributable risk	Difference between the *Risk* in an exposed population (*Absolute risk*) and the *Risk* in an unexposed population (*Reference risk*) [c.f. *Relative risk*] Synonym: Excess risk Note: attributable risk is the result of an absolute comparison between outcome frequency measurements, e.g. *Incidence*. Example: the attributable risk is calculated as [A/(A + B)] − [C/(C + D)] where the exposed persons with an outcome are A, the exposed persons without the outcome are B, the unexposed persons with the outcome are C, and the unexposed persons without the outcome are D If the *Incidence* of rash in a population treated with medicine X is 35/1500 = 0.023, and the *Incidence* of rash in a population who is not treated with X, during the same time period, is 5/2000 = 0.0025, the attributable risk is (35/1500) − (5/2000) = 0.0205 See also *Incidence* and *Prevalence*
Benefit-risk analysis	Examination of the positive and negative results of undertaking a specific course of action
Consumer	Not defined The use of the term 'consumer' can be misleading. A person may or may not be an actual consumer of *Healthcare* or medicines at a given time, but all members of the *General public* are potential consumers. For the latter group, the term *General public* is used instead of consumer. The term *Patient* is used when referring to actual consumers of medical or *Healthcare resources*
Continuing education	Enhancement or expansion of an individual's knowledge or skills by further schooling, usually after formal education has ended
Developing country	In the process of moving towards the economic and social model of the longer established industrialised countries Note: the term 'developing country' represents a concept that does not lend itself to a precise definition. The use of 'developing country' often reflects a value judgement, and the term refers to a large number of countries that are not homogenous. In some situations, it might be useful as a grouping term, although, when possible, more specific descriptors should be used. For *Pharmacovigilance* communication, the following characteristics are important: (i) insufficient funds for public health; (ii) insufficient access to medical care; (iii) insufficient control of quality and distribution of medicines; (iv) illiteracy or language problems in relation to medical and *Healthcare* communication
Drug	See *Medicinal product*
Effective	Achieving the desired result
Efficient	Producing a result with the minimum wasted effort
Equity	System of justice supplementing or prevailing over common and statute law
General public	People collectively as members of the community Synonym: the public

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Table I. Contd

Term	Definition
Harm	Damage qualified by measures of frequency of occurrence, severity or duration (c.f. *Risk*)
Healthcare	Maintaining, restoration or improvement of health by *Health professionals*
Healthcare professional	See *Health professional*
Health professional	Person who is trained and licensed to provide *Healthcare* to humans Synonym: healthcare professional Includes: doctor, nurse, dentist, pharmacist, midwife Excludes: veterinarian
Incidence	Number of new cases of an outcome which develop over a defined time period in a defined population at *Risk* Note: incidence is a frequency measurement of outcome development over time (c.f. *Prevalence*). A cumulative incidence is a *Proportion* (new cases divided by total population), often expressed as a percentage, and with the time period specified. The incidence is also commonly calculated as a *Rate* (new cases divided by total person-time of observation) Example: the incidence is calculated as A/(A + B), where the exposed persons who develop an outcome during the time period are A, and the exposed persons who do not develop the outcome during the time period are B. If 2500 people are treated with medicine X, and 30 of them develop an *Adverse reaction* in a year, the incidence of that *Adverse reaction* is 30/2500 per year, or 12/1000 person-years See also *Absolute risk*, *Reference risk*, *Attributable risk* and *Relative risk*
Indication	Remedy or treatment that is suggested by the symptoms as advisable or necessary
Liability	Condition of being accountable by law or *Equity*
Media	Means of communication Note: this term includes any means of communication, and may also refer to those engaged in them (see also *Mass media*)
Mass media	Main means of communication to the *General public* Includes: newspapers, radio, television and the Internet. Also includes journalists, editors etc. Working for organisations engaged in such communication
Medicinal product	Product intended to be administered to humans for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions Synonym: medicine Note: for the purpose of this document, the term 'drug' should be interpreted as equivalent to the concept medicinal product
Medicine	See *Medicinal product*
Medicine user	Person who is taking a *Medicinal product* for an approved indication Synonym: user Note: the concept of medicine user includes *Patients* taking medicines, as well as self-medicating individuals
Non-prescription medicinal product	*Medicinal product* available to the public without a *Prescription* Synonyms: non-prescription medicine, non-prescription product, over-the-counter medicine (OTC) Note: non-prescription medicinal product is a concept that covers *Medicinal products* generally available, as well as those that are available only from pharmacies (see *Pharmacy-sales-only medicinal product*). In some countries, all *Medicinal products* are pharmacy sales only
Odds	Probability of an occurrence p divided by the probability of its non-occurrence $(1 - p)$ [c.f. *Risk*]
Odds ratio	Ratio of the *Odds* in a given population and the *Odds* in another population Note: in case-control studies the odds ratio is the *Odds* of exposure (to a *Medicinal product*) in cases (e.g. individuals with an *Adverse reaction*) divided by the *Odds* of exposure in controls (e.g. individuals without the *Adverse reaction*). The odds ratio provides an estimate of the *Relative risk*

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Table I. Contd

Term	Definition
Patient	Person awaiting or under medical care or treatment by a *Health professional* Excludes: individuals who are self-medicating (see *Medicine user*) Note 1: this definition is wider than most standard definitions of patient in that it includes people who are not ill or injured, e.g. individuals who are prescribed *Medicinal products*, the *Indications* for which are not a disease or prevention of a disease (e.g. oral contraceptives). However, in relation to *Pharmacovigilance* communication issues, it is useful to have one term that covers all individuals who are in contact with *Health professionals* Note 2: it has been argued that the linguistic connotation of patient is a passive sufferer and that the word therefore should not be used. On the other hand, it can be argued that modern usage of the word has expanded its meaning to cover active individuals who can and will act as equal partners, and that, in the absence of another generally accepted term that covers the concept described in the paragraph above, patient is the preferred term to use
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems (WHO, 2002)
Pharmacy-sales-only medicinal product	*Medicinal product* available to the public only from pharmacies
Player	Individual, or group of individuals, with a legitimate interest and responsibility in a human endeavour, e.g. *Pharmacovigilance*
Postgraduate	Course of study carried on after graduation, especially after taking a first degree
Prescribe	To indicate a *Medicinal product* to be administered, usually done by writing a *Prescription*
Prescriber	*Health professional* licensed by law to *Prescribe* Note: a prescriber may have a limited licence, for instance allowing *Prescription* of certain categories of *Medicinal products*, e.g. in some countries midwives are licensed to *Prescribe* only oral contraceptives
Prescription	Direction or order for dispensing and administering *Medicinal products*, issued by a *Prescriber*
Prescription-only medicine	*Medicinal product* available to the public only upon *Prescription*
Prevalence	Number of existing cases of an outcome in a defined population at a given point in time Note: prevalence is a frequency measurement of an outcome existing at a given time (c.f. *Incidence*). It is calculated as a *Proportion* (cases divided by total in population), often expressed as a percentage Example: the prevalence is calculated as A/(A + B), where the persons who have an outcome are A, and the persons who do not have the outcome are B. If 450 persons have asthma in a town of 5000 people, the prevalence of asthma in that town is 450/5000 = 0.09 See also *Absolute risk*, *Reference risk*, *Attributable risk* and *Relative risk*
Proportion	Number of cases of an outcome divided by the total number of individuals in the studied population Note: a percentage is the proportion (cases divided by total in population) multiplied by 100 Example: a study population of 3500 people is taking medicine X. In a year, 22 of the individuals develop *Adverse reaction* Y. The proportion is 0.006 (22/3500); the percentage is 0.6% (22/3500) $\times$ 100 See also *Incidence* and *Prevalence*
Rate	Number of cases of an outcome divided by the total person-time of observation Note: a rate figure normally has a large whole number as a multiplier, reflecting the actual, or a scaled-up, population (e.g. 1000, 10 000, 20 000) Example: a study population of 3500 people is taking medicine X. In a year, 22 of the individuals develop *Adverse reaction* Y. The rate is 22/3500 person-years, which equals 63/10 000 person-years (22/3500 $\times$ 1) $\times$ 10 000 See also *Incidence* and *Prevalence*

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Table I. Contd

Term	Definition
Reference risk	*Risk* in a population of unexposed persons (c.f. *Absolute risk*) Synonym: baseline risk Note 1: reference risk can be measured over time (see *Incidence*) or at a given time (see *Prevalence*) Note 2: the unexposed population refers to a reference population, as closely comparable with the exposed population as possible, apart from the exposure See also *Attributable risk* and *Relative risk*
Relative risk	Ratio of the *Risk* in an exposed population (*Absolute risk*) and the *Risk* in an unexposed population (*Reference risk*) [c.f. *Attributable risk*] Note: relative risk is the result of a relative comparison between outcome frequency measurements, e.g. *Incidences* Example: the relative risk is calculated as [A/(A + B)]/[C/(C + D)] where the exposed persons with an outcome are A, the exposed persons without the outcome are B, the unexposed persons with the outcome are C and the unexposed persons without the outcome are D If the *Incidence* of rash in a population treated with medicine X is 35/1500 = 0.023, and the *Incidence* of rash in a population that is not treated with X, during the same time period, is 5/2000 = 0.0025, the relative risk is (35/1500)/(5/2000) = 9.3 See also *Incidence* and *Prevalence*
Risk	Probability of developing an outcome Note 1: the term 'risk' normally, but not always, refers to a negative outcome Note 2: contrary to *Harm*, the concept of risk does not involve severity of an outcome See also *Absolute risk*, *Reference risk*, *Attributable risk* and *Relative risk*
Signal	Reported information on a possible causal relationship between an *Adverse event* and a drug, the relationship being unknown or incompletely documented previously (WHO, 1991) Note 1: a signal is an evaluated association that is considered important to investigate further Note 2: a signal may refer to new information on an already known association Note 3: usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information
The public	See *General public*

Pharmacovigilance is an area that has undergone much development in the last decade, and safety issues are deservedly receiving much more attention, also from a wider audience, than in the past. As the scope of a field changes, so do the associated language and expressions: new concepts are introduced and jargon develops. Without agreed definitions and consistency in the use of terms, the situation can become very confused. Also, old definitions need review: terms such as 'adverse reaction' and 'adverse event' are still used, sometimes interchangeably. It can be argued that since the distinction between the two terms is not clear, another way of expressing the different concepts should be found.

An important challenge is to reach international agreement on the use of terms in the signal detection area. Different terms and expressions are used for the same concept (e.g. 'signal detection' and 'signal generation') and, conversely, the same term often does not mean the same thing when used by different people: 'signal' is a prime example of the latter. Furthermore, with the introduction of new data-mining methods, and new players previously not involved in pharmacovigilance, new terms and expressions will continue to be launched. Such a term is 'signal of statistical disproportionality'. If this term were to be widely accepted, it seems possible that it would add to the disagreement over the definition of the root term 'signal', or hopefully the reverse, and instead allow for new agreement. Whichever, the way one uses 'signal' as a stand-alone term needs to be altered.

In the light of these issues, the definitions in table I should be seen as a starting point for debate and discussion and not a final, exhaustive list. Ideally, each term that is commonly used in pharmacovigilance should be considered critically: are the concepts valid, how should they be denoted, can there be agreement on a preferred term that every-

one will use and what are the correct definitions? If broad international agreement can be achieved, the resulting greater clarity of communication should benefit all who are engaged in pharmacovigilance activities.

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References

1. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf 1994 Feb; 10 (2): 93-102
2. World Health Organization (WHO). The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: WHO, 2002
3. Uppsala Monitoring Centre (UMC). Dialogue in pharmacovigilance – more effective communications. Uppsala: UMC, 2002

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