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Guide on the interpretation of spontaneous case reports of suspected adverse reactions to medicines

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**Note: update of the existing guide on how to interpret adverse drug reaction (ADR) data that is included on the adrreports.eu portal (i.e. the public access to EudraVigilance data) as a result of the enhanced website being made available in late 2017.*

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1. Introduction

This document provides guidance on how to interpret information on spontaneously reported cases of suspected adverse reactions to medicines. It also gives an overview of current pharmacovigilance systems put in place to monitor the safety of medicinal products.

2. Definition of adverse reaction

An adverse reaction is a response to a medicinal product which is noxious and unintended [1]. Commonly, this is referred to as a "side effect" or "undesirable effect", while, in contrast, an adverse event may or may not be caused by a medicine.

3. Key considerations

- The reporting of cases of suspected adverse reactions seen in individual patients is a fundamental process underpinning pharmacovigilance.
- Spontaneous reporting is an important mechanism for healthcare professionals and consumers to communicate suspected adverse reactions to medicines regulatory authorities or pharmaceutical companies. These reports can generate signals of potential safety issues but alone are rarely sufficient to confirm that a certain undesirable effect in a patient has been caused by a specific medicine.
- The fact that a suspected adverse reaction has been reported does not necessarily mean that the medicine has caused the observed effect as this could have also been caused by the disease being treated, a new disease the patient developed, or by another medicine that the patient is taking.
- A single case report should be seen as a piece of a jigsaw puzzle, where further data are usually needed to complete the picture. These include e.g. data from worldwide spontaneous case reports, clinical trials and epidemiological studies. Causality assessment and interpretation of case reports is therefore performed in the context of all relevant data available.
- The number of reports of a suspected adverse reaction per se is not sufficient for assessing the likelihood that the reaction was caused by a particular medicine. Other factors need to be considered such as the background incidence of that suspected adverse reaction, the extent and conditions of use of the medicine, the nature of the reaction as well as public awareness. This information should be taken into account when interpreting numbers of case reports to avoid misleading conclusions regarding the safety profiles of medicines.

4. Monitoring the safety of medicines

No medicine or vaccine is completely free of risks. All medicines are authorised on the basis that the likely benefit outweighs the potential harm. For a marketing authorisation to come to this conclusion, data from clinical trials conducted during the development of a medicine are assessed. However, adverse reactions, which occur rarely or after a long time, may become apparent only once the product is used in a wider population. In addition, the benefits and risks of a medicine used in routine healthcare where patients may have more than one disease or treatment can usually not be studied before authorisation.
Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. The evaluation of the benefit-risk balance of a medicine may change over time with the increase in knowledge gained from its use by many people and the availability of new therapeutic alternatives.
The monitoring of the safety of medicines is called pharmacovigilance, which has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [2].

5. Reporting of suspected adverse reactions

The reporting of cases of suspected adverse reactions seen in individual patients is a fundamental process underpinning pharmacovigilance. This spontaneous reporting is triggered by a suspicion of a healthcare professional or a patient that observed signs and symptoms could have been caused by a medicine. Competent authorities in Member States encourage healthcare professionals to report their suspicions and observations of adverse reactions to medicines through national reporting systems.

Patients are also prompted by the information in the package leaflets to talk to their healthcare professional about any adverse experience associated with their treatment. Furthermore, the 2010 pharmacovigilance legislation provides the foundation for establishing systems for reporting by patients, carers and consumers across the whole European Union (EU). Patient reporting of suspected adverse reactions offers additional value to pharmacovigilance and provides useful information on the impact on patients' lives. These reports are also a valuable source for the detection of potential safety signals.

The national reporting systems in place ensure that reported cases are brought to the attention of the competent authority and the marketing authorisation holder (i.e. the company marketing the medicine) from where the cases are transmitted to EudraVigilance.

Most important is the spontaneous reporting of **serious** or **previously unknown** suspected adverse reactions. An adverse reaction is considered serious if it

- is life-threatening or has a fatal outcome;
- requires in-patient hospitalisation or extended existing hospitalisation;
- results in persistent or significant disability or incapacity; or
- is a congenital anomaly/birth defect.

In addition, there are other 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

(treatment) to prevent one of the other outcomes listed above. Examples of such events are allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room or at home as well as seizures/convulsions and serious blood dyscrasias (blood disorders) that do not result in hospitalisation. Important medical events are also regarded as serious suspected adverse reactions.

Spontaneous reporting for newly marketed medicinal products is also a priority, given the limited experience with such medicine.

6. Sources and assessment of safety signals

New information on a possible risk is called a signal [3]. Signals of previously unknown adverse reactions or changes in the severity, characteristics or frequency of known reactions may arise from various data sources, including spontaneous reports, clinical trials and epidemiological studies (including registry studies). Once a signal has been identified, investigations are necessary to refute or confirm and quantify the risk. These investigations consider the likelihood that the medicine caused or contributed to the effect, try to identify risk factors and estimate the frequency of occurrence. Assessment of signals takes into account possible errors in the use of the medicine or manufacturing defects.

7. Possible regulatory actions after assessment

Following the assessment of a safety signal, a decision on the most appropriate regulatory action is taken by the competent authorities. The decision may include:

- a request for (an) additional study(ies) from the marketing authorisation holder to gain further evidence on the matter;
- a change to the product information[1] to promote the safe use of the product, e.g. by adding warnings on signs and symptoms for healthcare professionals and patients, changing the dose recommendations or including new restrictions on the use of the medicine in a certain patient population;
- the suspension of the marketing of a medicine while investigations are ongoing;
- the withdrawal of the marketing authorisation for the medicine;
- no need for further evaluation or action at this point of time (the safety concern is followed through routine pharmacovigilance).

Information on the regulatory action is communicated to healthcare professionals, patients and the general public through established channels and timelines, which reflect the degree of urgency. The established channels include publications on websites, information provided to patient and healthcare professional organisations and the media as well as direct mailing of healthcare professionals.

8. Public access to case reports

Reporting systems at national and EU level comply with data protection legislation, and therefore the data contained in the databases of national competent authorities and EudraVigilance are anonymised appropriately and are not available in full to the public. EudraVigilance [4] is a database maintained by

[1] The product information consists of the medicinal product name, the summary of product characteristics, the package leaflet for the patient and the label on the packaging.

the European Medicines Agency in collaboration with national Competent Authorities in the EU, which brings together suspected adverse reactions reported within the EU as well as reports from outside the EU submitted by marketing authorisation holders in accordance with EU legislation. A EudraVigilance Access Policy is in place on public access to these data without jeopardising data privacy [5]. The public access is provided at http://www.adrreports.eu/.

Anonymised case reports or a report on a series of anonymised observed cases are also sometimes published in the scientific literature by healthcare professionals.

9. Further information

Details on the measures and processes for the conduct of pharmacovigilance in the EU can be found in the Good Pharmacovigilance Practices (GVP)[6], in particular GVP Module VI "Management and reporting of adverse reactions to medicinal products", GVP Module IX "Signal Management".

10. References

[1] Article 1 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use: Official Journal of the European Union; OJ L 311, 28.11.2001, p. 67. Available under:
http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

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[3] CIOMS Working Group VIII. Practical aspects of signal detection in pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences; 2010.

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