



European Public Health Alliance (EPHA)

Position Paper on Pharmacovigilance

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EPHA is the European Platform bringing together public health organisations representing health professionals, patients groups, health promotion and disease specific NGOs, academic groupings and other health associations. Our membership includes representatives at international, European, national, regional and local level.

EPHA's mission is to protect and promote public health in Europe.

EPHA brings together organisations across the public health community, to share learning and information and to bring a public health perspective to European decision-making. We help build capacity in civil society participation across Europe in the health field, and work to empower the public health community in ensuring that the health of European citizens is protected and promoted by decision-makers. Our aim is to ensure health is at the heart of European policy and legislation.

Please see www.eph.org for more information.

Pharmacovigilance- General Observations

Pharmacovigilance encompasses surveillance of side effects of medicines after short-term and long-term use. After a new medicine is introduced into the market, pharmacovigilance is particularly important, as comparatively little is known about its safety profile until it has been exposed to a larger, more diverse population than clinical trials participants. Some new medicines are given “conditional authorisation” to be sold on the market even though the risk / benefit profile is unclear. In these cases, pharmacovigilance is particularly crucial to detect adverse drug reactions, to minimise patient exposure to harm when a problem is detected.

Pharmacovigilance is an observational science undertaken through a variety of means, including the collation and analysis of data received from direct reporting of adverse drug reactions by patients or healthcare professionals. In the majority of the EU Member States, adverse drug reaction reporting is done by healthcare professionals solely, but a selected number of countries also have direct reporting by patients to the health authorities or to other designated bodies (France, Denmark, Sweden, The Netherlands, UK).



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Throughout Europe, the general level of reporting of adverse reactions has been very low¹. Around an estimated 10-25 per cent of reactions experienced by patients are reported and it has also been documented that these are usually the side effects that are already reasonably well known.

The human and financial costs of the adverse effects of drugs are high, and are borne by society: adverse effects are responsible for at least 5% of hospital admissions and the 5th ranking cause of hospital deaths according to the European Commission².

Pharmacovigilance in Europe needs to be strengthened:

- The vast majority of new medicines that are brought to the market provide no real therapeutic advance³. The comparison between the benefit- risk balance of a newly developed medicine and that of existing medicines must be a strong component of the market authorisation process.
- The post-marketing follow-up of harm caused by medicines has been mainly passive, patients and health professionals have not been encouraged to report side effects. In some EU Member States, the reporting of adverse events by healthcare professionals is not mandatory, which may partially explain the poor feedback.
- Pharmacovigilance hinders the pharmaceutical industry commercial interests which explains sometimes its reluctance to support reporting on side effects and the often observed lack of transparency from the industry about post-authorisations trials.
- Knowledge about the adverse effects that medicines have on patients is a matter of public interest. All medicines' safety information should be publicly accessible in the best interests of public health.
- The level of transparency concerning pharmacovigilance data, including periodic safety update reports (PSURs), and how decisions about market authorisations or withdrawals are made at the EMEA, is insufficient. The pretext given, that this scientific information is "commercially confidential" and thus, kept out of the public domain can be irrational, irresponsible and unjust.

¹ Salustest, April 20018, The Lancet, December 20019, Consumentenbond, June 200210, UK National Audit Office, January 200311

² Examples from recent years include rofecoxib (Vioxx[®]) with fatal cardiovascular events, selective serotonin reuptake inhibitor antidepressants (fluoxetine (Prozac[®]), paroxetine (Deroxat[®]/ Seroxat[®]) and others) and rimonabant (Acomplia[®]) with increased suicide risk, olanzapine (Zyprexa[®]) with diabetes and metabolic disorders, and rosiglitazone (Avandia[®]) with fatal cardiac disorders.

³ Prescrire Editorial Staff "Prescrire's ratings of new products and indications over the last 10 years" *Prescrire Int* 2009; 18 (100): 85.



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- There is a clear issue to do with independence and a possible conflict of interests in the way medicines regulatory agencies act as service-providers to pharmaceutical companies seeking market authorisations for their products. Pharmaceutical companies are the main clients of the medicines regulatory agencies, the former funding the latter through the fees they pay⁴. And many of the experts consulted by the medicines regulatory agencies are also often working for pharmaceutical companies⁵;
- There have been unacceptable delays in withdrawing problem medicines from the market after serious adverse effects have been reported.⁶
- National and regional pharmacovigilance systems are well-adapted bodies, attuned to the intricate collection and analysis of adverse drug reaction data that leads to timely alerts and interventions to protect population health⁷. National and regional centres manage to bring problems to light through the expertise of teams specialised in pharmacology, who are able to assess the causality of the adverse events reported due to their proximity to both the population and healthcare professionals. This proximity, in terms of language and knowledge of the lifestyle and habits of patients, enables easy contact with reporters, for example by telephone. Teams can thereby obtain valuable additional information, building up the scientific data contained in the original report and making it more informative⁸. Without this step, incomplete reports cannot be properly analysed, and the information they contain is lost.
- European pharmacovigilance systems have a number of limitations: reporting of adverse reactions by healthcare professionals, patients (in some cases) and pharmaceutical companies is not systematic; the analysis of

⁴ For example, the EMEA's 2008 annual report reveals, on the line labelled "services rendered", that it collected close to 139 million euros in fees from drug companies, which represents 74% of its revenue (and this percentage is constantly increasing).

⁵ The case of erlotinib (Tarceva[®]) from the company Roche is a prime example. After having obtained a marketing authorisation for certain types of lung cancer, the company Roche requested the addition of advanced or metastatic pancreatic cancer. Initially the new indications were refused by the EMEA's drug licensing committee (CHMP) in July 2006. After the company challenged the decision, the EMEA set up a group of 4 experts at the end of 2006, which then approved these indications. However 3 of the 4 experts had connections with Roche on this sensitive application.

⁶ For instance in the cases of nimesulide(**g**), rimonabant(Acomplia[®]) (**h**), and rofecoxib (Vioxx[®]) (**i**).

⁷ For example, the withdrawal of the combination dextropropoxyphene+ paracetamol by several EU countries in 2005, or nimesulide from 2002) (**f**).

⁸ For example, it was a Spanish team from a regional centre that discovered (by analysing over one hundred reports) that trimetazidine causes parkinsonian syndromes that are reversible on withdrawal of the treatment. This adverse effect was unexpected as trimetazidine is a substance attributed with "antioxidant" properties and a "cytoprotective" effect on the heart. This result was confirmed by several French regional pharmacovigilance centres. This information averts erroneously diagnosing Parkinson's disease in many patients taking trimetazidine: their trimetazidine therapy just needs to be stopped (in any case its efficacy was challenged by several Member States in the arbitration procedure).

Stopping this treatment, whose risk-benefit balance is clearly unfavourable, avoids having to initiate treatment for Parkinson's disease, which in turn causes many additional adverse effects.



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pharmacovigilance data can be delayed; surveillance instruments, passive and not proactive, are inadequate. In some countries, patients and consumers organisations often feel compelled to plug the gaps. There is little awareness among the public about pharmacovigilance activities and the importance of reporting adverse events. There is a need for a public information programme to encourage greater public engagement, good systems to allow patient reporting directly, and for a reinforcing and improvement of systems for professional reporting, together with a professional culture change so that reporting becomes accepted and routine.

- Transparency of the management of medicines safety issues in Europe must be ensured. Optimal harm reduction cannot be guaranteed unless access to information about adverse drugs reactions by patients, health professionals and citizens in general is improved.

How to improve pharmacovigilance?

Pharmacovigilance in Europe can be stimulated by:

More stringent requirements for safer market authorisations

A new application for marketing authorization should demonstrate that the new drug offers added therapeutic value with minimal risk of side effects, to avoid unnecessary exposure of the population to otherwise preventable harm. Such a requirement would redirect research and development to areas of unmet medical needs. It would represent an effective tool to end the current waste of resources, whereby large sums from the national health budgets are spent to finance, at high prices, medicines that offer no added therapeutic value or are even therapeutic regression.

Enhanced communication with the public and patients

Public information and education campaigns, through the EMEA and national agency websites, health centres and patient organisations, etc., on the importance of adverse drug reactions reporting should be carried out and it should be a key part of training for health professionals. Contact between local pharmacovigilance centers and patients and consumer organisations should be fostered to elicit meaningful feedback from patient and consumer groups in order to improve the direct patient reporting system. Internally, the EMEA should define a communication policy and discuss on when and how to communicate in order to improve the rational use of medicines.

Improve patient information leaflets

Patient information leaflets need to be designed to convey potential adverse reactions more clearly, so that the relative likelihood of these occurring is included and people know what to do if adverse reactions occur. Key points could be highlighted on the patient information leaflet in a different font type (in bold for example). Where national systems allow patients to directly report the suspected



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side-effects of their medicines the means for doing this should be included in the leaflet together with the recommendation to discuss them with their health professional.

Introduce a symbol to indicate new medicines under surveillance

Patient information leaflets and packages should carry an internationally agreed symbol if a medicine has been on the market for less than five years or is under intensive surveillance for any other reason, such as in cases of “conditional market authorisation”, in order to help identify drugs which have been authorised despite insufficient evidence. The statement “*This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to <name and web-address of the national competent authority and discuss with your healthcare professional>*” could be included with the pictogram already widely used in the European Union -a black triangle pointing downwards (Δ)- next to the brand name on each box and on immediate packaging.

EMA should furthermore continuously discuss with patients, health professionals and consumer organisations how to best communicate medicine related risks and how this should be reflected on the package and the patient information leaflet.

Emphasising the professional obligation of health professionals to report across the EU

The systems allowing health professionals to report adverse drug reactions (including the computer software systems) should be strengthened by putting greater emphasis on the professional obligation of healthcare professionals to report adverse reactions at all stages of a medicine’s life. Moreover, current obstacles prohibiting community pharmacists to report adverse drug reactions (such as the ones in Sweden) should be removed.

Encourage direct reporting of ADRs by patients and healthcare professionals

Conduct active searches for adverse reactions, which would involve patients and carers as responsible players, possibly through well-conducted prospective surveys. Feedback to healthcare professionals and patient reporters is also important to demonstrate the value of the information that they submit on adverse reactions. Moreover, understanding that reporting is time-consuming for healthcare professionals, Member States should support them by providing the adequate tools, such as e-health technology to facilitate data collection.

Improved Europe-wide collection of high-quality adverse event reports

Reports from patients, healthcare professionals and pharmaceutical companies must be collected and centralised by independent pharmacovigilance systems in each Member State. This also requires that pharmaceutical companies systematically and exclusively send the reports they collect to these independent pharmacovigilance systems. The independent pharmacovigilance systems will then be responsible for sending the data (to which valuable information based on their particular expertise



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could be added) to the Eudravigilance database, to ensure the high quality of the content of Eudravigilance. The data must be made available, in a usable format, to all Europeans.

Opt for rigorous pre-authorisation studies in place of post-authorisation risk management systems

Unjustified conditional marketing authorisations must not become the norm, even when accompanied by risk management systems and post-authorisation studies. Such practice would expose patients to adverse effects which could be undetected or underestimated at the time of the marketing authorisation. Risk management systems will only be able to reinforce pharmacovigilance if designed and conducted under health authorities' close supervision. Risk management systems aims should be to identify any adverse effects, as well as their frequency and severity (also long-term),

Monitoring and controlling post-authorisation studies, including those pertaining to "risk management systems" should be made mandatory. These studies must be conducted by independent teams and should not be used as an excuse for granting premature marketing authorisations;

Improve transparency

The EU population has the right to access medicines safety information for any medicine which is on the market. This can be achieved by granting total public access to pharmacovigilance information, including PSURs and data on medicines' consumption, complete PSUR assessment reports, Eudravigilance reports as well as periodic summaries prepared by the EMEA, and requests for post-authorisation studies or risk management programmes together with the pharmaceutical companies' responses. EPHA however welcomes the decision to make data contained in EudraCT public⁹.

Information which is relevant to public health should be disclosed to all Europeans and not only to a selected stakeholder or professional group.

The discussions and decisions inside EMEA pharmacovigilance committee meetings or other working parties are of public interest and value. The following information should be made public: the agendas and full transcripts of meetings of the European pharmacovigilance committee and the detailed rationale behind pharmacovigilance decisions, including minority opinions and the detail of votes.

Provide authorities with the means to act independently from industry

⁹ The EudraCT database, hosted by the European Medicines Agency (EMA) will make all data related to the application for authorisation and progress of all clinical trials taking place in Europe open to the public, by November 2009. For more, see: <http://www.eahp.eu/EAHP-EU-Monitor/Information-on-Clinical-Trials-to-be-made-public>



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The analysis of adverse effects and the re-evaluation of the risk-benefit balance of medicines must be entrusted by the public authorities to working parties composed of experts who are independent of both the pharmaceutical companies and the licensing committees, with complete transparency.

Reinforce the public expertise of the national and regional pharmacovigilance centres

Guarantee public funding for the European Pharmacovigilance Committee and the national and regional pharmacovigilance systems of Member States, in order to allow them to fulfil their responsibility for protecting the population. The effectiveness of their work will lead to more timely decisions (i.e. strengthened monitoring or market withdrawal of medicines found to have an unfavourable risk-benefit balance), and consequently important savings will be made (i.e. reduction of the numbers of hospital admissions, days of sick leave, and medical consultations caused by the adverse reactions due to these medicines).

Stimulate additional longer-term research on specific medicines

Clearly define the level of information needed by requesting more thorough assessment of unexpected side effects during the development of medicines. In order to focus on the potential long-term effects of medicines and to supplement spontaneous reporting from healthcare professionals, EMEA should stimulate additional research that follows a selected group of patients using specific medicines. The aim of this research would be to identify potential slow to emerge adverse reactions and any other difficulties with use of the medicine over time. Consideration of issues related to gender, ethnicity, genotype, age or any other differences and interactions with over the counter medicinal products, diet and “recreational drugs” should also be better defined.

Encourage twinning of knowledge transfer in pharmacovigilance between countries

A pairing/twinning system of knowledge transfer between countries in pharmacovigilance should be put in place. The information reaching the Eudragilance will be filtered and it is fundamental to guarantee it has sufficient quality to enable an appropriate analysis. Local and national pharmacovigilance systems need to be further supported in order to ensure that the transfer of high quality data is not impaired.