



European Public Health Alliance (EPHA)

Briefing Note on Pharmacovigilance

Subject	EPHA Briefing Note on Pharmacovigilance
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Background

In the EU, new medicines are licensed to be sold on the European market (“market authorisation”) by the Community-wide European Medicines Agency (EMA) and by Member States’ own drug regulatory agencies (“competent authorities”). The EMA handles market authorisation applications for medicines seeking a licence for more than one European country. Medicines to be marketed in only one European country apply for authorisation from that Member State.

To gain a market authorisation, a newly developed medicine must demonstrate efficacy, safety and quality in clinical trials, and demonstrate a favourable benefit to risk ratio. The evaluation of medicines prior to marketing authorization only provides a general idea of their adverse effects, because the medicines have been tested for a limited time on a selected sample of clinical trials participants (volunteers and patients). Some adverse drug reactions (ADRs) only arise after long-term use in a larger population, sometimes under unique circumstances or in the presence of co-existing treatments.

The role of pharmacovigilance is to obtain further knowledge of adverse effects that arise after a medicine is marketed in order to limit the harm to patients and consumers. Pharmacovigilance entails medicines safety monitoring, in which the safety of patients is the top priority. The system is largely driven by spontaneous reporting of suspected adverse drug reactions by healthcare professionals and (in some countries) patients to drug regulatory authorities and/or and pharmaceutical companies. Pharmacovigilance systems must be carefully attuned to the patients’ experience in order to detect unexpected, idiosyncratic, or rare adverse drug reactions that have the potential to be very serious.

The WHO- World Health Organisation (2002) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”.

Adverse drug reactions can be serious and the human and financial costs of the adverse effects of medicines are high. Adverse effects are responsible for at least 5% of hospital admissions and the 5th ranking cause of hospital deaths according to the European Commission¹. The WHO Uppsala Monitoring Centre estimates that 4% to 5% of marketed medicines are withdrawn due to safety concerns. On occasions, alerts from ADRs are not acted on quick enough and patients experience exacerbated adverse effects. Recent examples include rofecoxib (Vioxx®), a painkiller with cardiovascular side effects in 2004 and rimonabant (Acomplia®) an anti-obesity drug with psychiatric side effects in 2008.

¹ Examples from recent years include rofecoxib (Vioxx®) with fatal cardiovascular events, selective serotonin reuptake inhibitor antidepressants (fluoxetine (Prozac®), paroxetine (Derogat®/ Serogat®) and others) and rimonabant (Acomplia®) with increased suicide risk, olanzapine (Zyprexa®) with diabetes and metabolic disorders, and rosiglitazone (Avandia®) with fatal cardiac disorders.



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Some ADRs are already known to health care professionals and can generally be managed by a clinician e.g. by closely monitoring the therapy, adjusting and reducing doses, switching to different medicines with the same effect (for example, using blood pressure lowering medicines from a different pharmacological class) or treating the side effect (for example, by using laxatives for constipation caused by morphine).

Periodic Safety Update Reports (PSURs) are used to re-evaluate safety post-marketing and are prepared by the drug companies to be delivered to the drug regulatory authorities.

The Proposed Pharmacovigilance Directive and Regulation

The EU Pharmaceutical Package proposes a centralised pharmacovigilance system that makes greater use of risk management systems. According to the proposal, it is proposed that a marketing authorization can be granted provided that post-authorisation studies are to be conducted (this condition has to be stated in the risk management plan)². But every time the health authorities want to ask for a risk management system or post-authorisation study to be carried out, they will need to seek the opinion of the producer before confirming their request³⁴.

The Commission proposes to support a central pharmacovigilance database, based around the existing Eudravigilance database, which would potentially allow better detection and analysis of rare adverse events through its increased size, and avoid duplicate analysis by multiple national authorities.

The Commission proposes that pharmaceutical companies receive healthcare professionals' and patients' adverse drug reaction reports⁵. Companies will be responsible for sending these reports to "a single point within the Community"⁶ (i.e. Eudravigilance database). This arrangement provides an opportunity for drug companies to manipulate the data before independent analysis.

It is also proposed that Member States may hand over the "follow up of such [PSUR] reports" to drug companies⁷. In this case, pharmaceutical companies would be both defendant and jury charged with assessing the change, if any, in their product's risk-benefit balance⁸. The subcontracting of data interpretation to drug companies is a major

² proposed article 22a of the Directive and article 10a of the Regulation

³ proposed articles 22a and 104a of the Directive

⁴ There are no plans however to provide public access to the health authorities' detailed requests or the drug companies' responses that influence the confirmation and final content of these requests. Yet these documents are extremely informative, as illustrated by the US experience with paediatric studies for which requests are publicly accessible on the FDA website, accompanied by the modifications requested by the pharmaceutical companies.

⁵ proposed article 107(1) and (2)

⁶ proposed article 107(1)

⁷ proposed article 107(4)

⁸ proposed article 107b which stipulates that the "scientific evaluation of the risk-benefit balance of the medicinal product" be produced by pharmaceutical companies in their periodic safety update reports (PSURs)



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limitation in the current pharmacovigilance system. Enlarging these subcontracting arrangements would further endanger patients by stripping the health authority of their authority, expertise, credibility and autonomy.

The directive requests that Member States establish web-based reporting portals through their competent authorities, and make it possible for patients as well as healthcare professionals to report ADRs. The directive asks Member States to encourage healthcare professionals to report ADRs and suggests that Member States create powers to compel healthcare professionals to report event, if this is felt necessary.

A new Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) would be established in the EMEA, reporting to the Committee on the Use of Medicinal Products in Humans (CHMP). CHMP is responsible for the initial risk assessment of a new medicine and the decision to grant or refuse a marketing authorisation. The current EU Commission's proposal foresees that a European Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) will replace the Pharmacovigilance Working Party⁹, reviewing safety concerns of marketed medicines without the authority or resources to enact their recommendations. The only real advance of the proposed PRAAC is that, as part of the EU pharmacovigilance procedures, the PRAAC would be able to organise public hearings, which would enhance transparency¹⁰.

The proposal allows for the EMEA to request a post-marketing safety study be undertaken by the pharmaceutical company in response to concerns about a medicine, with submission of an abstract and full report to the EMEA.

The centralisation of pharmacovigilance activity would also include streamlining PSURs, so that pharmaceutical companies produce a central report for the EMEA, rather than multiple reports (covering variable time periods). The frequency of PSURs, which can be contested by the pharmaceutical companies, is variable and determined by that which is "appropriate" to the drug's risk profile¹¹. Moreover, PSURs will no longer be required for longstanding products considered to have been in "well-established medicinal use" (for at least 10 years within the Community)¹².

The legislation is less prescriptive around the specifications of pharmaceutical company pharmacovigilance systems (currently set for the lifespan of a product as part of the marketing authorisation application).

The directive widens the definitions of reportable adverse events to include those which result from medication errors, overdoses, uses outside the product license and illicit use, rather than those simply occurring during routine licensed use.

The directive also changes the requirements for Summaries of Product Characteristics (SPCs or SmPC) – the detailed prescribing advice for each medicine – and the

⁹ proposed amendment to article 27 of the Directive and to article 56(1)(aa) of the Regulation

¹⁰ proposed article 107k(2) of the Directive

¹¹ proposed article 107c(6) point (c)

¹² proposed article 107b(3)



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requirements for the package inserts of information for patients. For both these items, the directive would add a box of key information for safe use of the product.

Cost Impact

The pharmacovigilance amendments are predicted to reduce costs for industry and increase costs for the regulators, but doesn't build on previous legislative changes further to the pharmaceutical review, which included provisions that pharmacovigilance activities should be funded through public funds. It is suggested that these costs are recouped by way of fees from industry.

Potential Issues and Improvements

Eudravigilance database

A sole, supra-national collection of reports such as the Eudravigilance database could dilute the data and deprive society of the expertise of pharmacovigilance centres in Member States concerning the adverse effects that occur within their own borders. A single European pharmacovigilance “mega-database” removed from local proximities cannot be sensitive to linguistic, geographic, demographic and life-style nuances that give valuable clues in the analysis of adverse events reports. In this way, a centralized database could undermine the expertise and authority of national and regional systems. While it is proposed that some pharmacovigilance centres could consult the Eudravigilance database, they will only access the registered data that is disconnected from contextual information needed to resolve the reports.

The Eudravigilance database must enable national health authorities to share their information and benefit from each others' work. The Eudravigilance database must not replace the local network currently composed by national and, in many countries, regional public pharmacovigilance systems. Local networks must be the entry point for data, if we are to preserve and benefit from their expertise.

Direct ADR reporting

Reports from either patients, healthcare professionals or drug companies must be collected and centralised by the 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 could be added) to the Eudravigilance database, to ensure the high quality of the content of Eudravigilance.

Industry strangle-hold over pharmacovigilance data

Data on adverse effects experienced by patients are public scientific data. They need to be analysed and interpreted to prevent recurrence.

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 drug companies and the licensing committees,



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with complete transparency. These working parties will be able to use all data available: reports received by the Pharmacovigilance centres from patients and healthcare professionals, well-documented case reports sent by pharmaceutical companies (raw data), published data recorded by the EMEA in Eudravigilance, etc.

It is reasonable for pharmaceutical companies to participate in data collection of their products' adverse effects, particularly during clinical trials or post-authorisation safety studies. But under no circumstances should companies be situated at the centre of pharmacovigilance, in a monopolistic position over other concerned parties.

Risk Management

Risk management systems must not be a means to lower pre-authorisation safety standards. Experience acquired over recent years shows that "risk management systems" are often used to reassure the public when inadequately evaluated drugs have been granted premature marketing authorisation. The examples of rimonabant (Avandia^o) and varenicline (Chantix^o/Champix^o) illustrate this point¹³. Based on their marketing authorisation applications, these 2 drugs should quite simply never have been authorised, which would have avoided the unnecessary exposure of the population to their serious adverse effects. Worse still, wider use of risk management systems, possibly accompanied by post-authorisation studies, appear to be grounds, in the medium term, for less thorough pre-authorisation evaluations¹⁴.

Risk management must not be left entirely to pharmaceutical companies, where clear conflicts of interest exist between complete disclosure of safety concerns and ongoing sales of products, but also be conducted or independently verified by the EMEA or competent authorities.

PRAAC

The PRAAC must be defined as a European instrument for cooperation between national pharmacovigilance systems, intellectually and hierarchically independent from drug licensing committees. It must be entirely financed by public funds. Its resources must be increased, to, at least, one representative per Member State, and its members should not have any conflicts of interest with pharmaceutical companies. Meeting transcripts must be made public, including voting details.

The European pharmacovigilance committee must have similar powers to the CHMP. After analysis and discussions of Member States' assessments performed under its supervision,

¹³ In the face of reports of adverse effects (increased suicide risk) and deaths after rimonabant (Acomplia^o) was licensed (a drug for obesity granted a European marketing authorisation on the basis of rather insubstantial data and poorly elucidated risks), the agencies' response was initially confined to setting up a "risk management system", which was not made public. After repeated requests, the assessment report on the risk management system, produced by the Swedish drug regulatory agency, was sent to the editorial staff of Prescrire (an independent drug bulletin): 65 of a total of 68 pages had been completely obscured! It took over 2 years after its marketing authorisation was granted for rimonabant to be withdrawn from the market due to an unfavourable risk-benefit balance in obesity. Similarly varenicline (Chantix^o/Champix^o), for which a risk management system was put in place, has an unfavourable risk-benefit balance in smoking cessation (withdrawal symptoms, psychiatric disorders including increased suicide risk, etc.).

¹⁴ As part of the consultation held on this subject in February 2008, the Commission had in fact presented this weakening of pre-authorisation evaluation as a means of boosting drug companies' competitiveness: "earlier product authorisation provides faster return on investment and, by reducing the cost of capital (through increased investor confidence), the total cost of product development is reduced" (section 3.2.1 of the introduction to the consultation of February 2008).



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the European pharmacovigilance committee must be able to propose decisions directly to the European Commission (namely pertaining to withdrawals or changes to marketing authorisations), without being subject to any censorship by the CHMP or CMDh.

The European pharmacovigilance committee must be sufficiently autonomous to carry out any research it deems necessary (proactive pharmacovigilance), rather than compelled to wait for the “alerts” by health authorities or pharmaceutical companies.

Transparency

Pharmacovigilance data are not commercial data to be collected by pharmaceutical companies as part of their marketing services. The assessment reports of the PSURs prepared by national health authorities and delivered to the European pharmacovigilance committee, must be made public (aa), including data on consumption, which is essential for evaluation of the level of exposure of the population.

The content of the Eudravigilance database at the European level, as well as the content of the national databases, must be publicly accessible, in user-friendly format. This will foster further research on adverse drug events by independent teams and also pharmaceutical companies who want to study the adverse effects of their drugs more thoroughly. The USA Food and Drug Administration (FDA) already provides this type of information through quarterly data extracts from its Adverse Event Reporting System (AERS) database.

There must be full transparency in how decisions are reached by EMEA and competent authorities. The minutes of Committee meetings must be detailed, in accordance with article 126b of Directive 2004/27/EC. The FDA’s publicly accessible “transcripts” (word-for-word transcription of the meetings) are a useful model. The detailed agendas for the meetings of Committees and working parties must be published online. These should be available, at the latest, by the day before the meetings take place, so that issues where a “final decision” was not obtained cannot be removed from the minutes.

Patient Information

The key information in SPCs and package leaflets needs to meet patient and consumer needs for an accessible yet complete information. Particular attention should be paid to vulnerable groups such as the elderly, pregnant women/unborn children, and people with multiple health conditions requiring treatment with a number of medicines. There may be better approaches to improving patient information leaflets.

Adverse effects and recent pharmacovigilance decisions should be identified, by highlighting the key points and including them on the patient information leaflet in a different font type (in bold for example). Drugs that have been authorised despite insufficient evidence should be identified by including 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>*”¹⁵, and also by including

15 proposed amendment of article 11 of the Directive



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the pictogram already widely used in the European Union -a black triangle pointing downwards- next to the brand name on each box and on immediate packaging

PSURs

Even for so called “well-established” medicines, periodic safety update reports (PSURs) must be submitted regularly, at least every 5 years. Dramatic examples of adverse effects (carcinogenicity, genotoxicity) discovered at a later stage are not rare, even 30 years after obtaining marketing authorisation¹⁶. By definition, marketing authorisation applications contain no long-term evaluation. Evaluation of the long-term effects of in-utero exposure to drugs is particularly weak.

¹⁶ One example is diethylstilbestrol (DES), which is responsible for uterine cancers and malformations in women exposed to this drug in utero while their mothers were pregnant. Its adverse effects were recognized 30 years later. Another example is valproic acid, which was recently discovered to cause neuropsychiatric disorders in children following in-utero exposure. A further example is all germander, a medicinal plant traditionally used for decades, but which has been established to be hepatotoxic. A final example is the combination dextropropoxyphene + paracetamol, which was withdrawn from the market in several countries in 2005 whereas its marketing authorisation was originally granted in the mid- 1960s.