

La revue Prescrire Contribution to Consultation on Pharmacovigilance in the EU

The new legislation must be fully applied, and improved where patient safety and public transparency is concerned

- **The new European legislation offers an opportunity to improve pharmacovigilance in the EU. But it must be applied in full, without delay, and be improved where necessary.**
- **This position statement is part of Prescrire's contribution to the public consultation on pharmacovigilance in the European Union.**
- **If it is to serve patients' best interests, pharmacovigilance must receive adequate public funding; public access to drug safety data must be facilitated; and the current confusion between the respective roles of the drug companies and regulatory agencies must be eliminated.**
- **To help healthcare professionals and patients to identify the most important and most recent warnings, the relevant sections of the SPCs should be highlighted.**
- **Real transparency means easier access to data from PSURs and EudraVigilance, for example, and clear justification for decisions based on pharmacovigilance data. "Commercial secrecy" must no longer serve as a pretext to hinder access to data on drug consumption.**
- **The health authorities, including regulatory agencies, must act mainly as patients and public health advocates, and stop serving drug companies' interest first.**
- **Drug companies' influence over pharmacovigilance guidelines and drug safety decisions must be reined in, given their evident conflicts of interest.**
- **Pharmacovigilance must henceforth be publicly funded, and no longer paid for solely through the fees that regulatory agencies charge to drug companies for their services. Sufficient funds must be made available to gather and analyse adverse drug reactions reported by members of the public; to exert effective public control over drug safety information; to oblige companies to conduct postmarketing studies on which their marketing approvals are conditional; to conduct independent pharmacovigilance studies; and to evaluate the impact of drug safety decisions.**
- **For safety-related marketing decisions to be made independently, a European Pharmacovigilance Committee needs to be established and endowed with the same authority as the Committee for Human Medicinal Products.**

On 15 March 2006, the European Commission launched a public consultation on the current functioning of pharmacovigilance in the European Union, as governed by the European Directive and Regulation on medicines for human use published in the Official Journal of the European Union on 30 April 2004 (1-3). As a preamble to this very welcome consultation, the European Commission issued a report on the current strengths and weaknesses of pharmacovigilance in Europe (4). Patients, healthcare professionals and pharmaceuticals firms are being invited to express their opinions and suggest improvements (3).

For its part, *Prescrire* notes that the new European regulatory framework is still not adequately applied, and that, as it stands, the new framework cannot be expected to create a system that fulfils public health requirements, as defined by the Berlin Declaration on Pharmacovigilance issued by the International Society

of Drug Bulletins (ISDB) in 2005 (5). Here are the main points of *Prescrire's* position statement on pharmacovigilance in the EU.

Transparency is a prerequisite for effective pharmacovigilance

Informing the public and healthcare professionals on pharmacovigilance issues has been one of the roles of the European Medicines Agency (EMA) since its creation, and is clearly spelled out in articles 57e and 57f of Regulation (EC) 726/2004. Yet in Spring 2006 EMA only allowed a trickle of drug safety information to escape from its bureaucratic clutches.

Identification of recent pharmacovigilance decisions. The reasons underlying changes in a drug's marketing approval because of safety concerns are still not fully explained by the European authorities. It would be helpful if at least the relevant parts of the summary of product characteristics were highlighted, so that healthcare professionals and patients can identify the most important and most recent decisions.

Easier access to PSURs. Companies are obliged to provide EMA and Member States with Periodic Safety Update Reports (PSURs) every 6 months for the first 2 years, every year for the following 2 years, and then every 3 years (instead of 5 years previously) (article 104.6 of Directive 2004/27/EC; article 24.3 of Regulation (EC) 726/2004). These reports must be accompanied by an assessment of the "*risk-benefit ratio*", but public access to these important data is not explicitly required in the current European rules (a).

Easier access to EudraVigilance. All information on adverse drug reactions must be recorded in a database (EudraVigilance), provided for by article 57 of Regulation (EC) 726/2004 and "*shall be permanently accessible to all Member States and without delay to the public*" (article 102 of Directive 2004/27/EC). It is also stated that data exchanges will be facilitated by electronic transmission of adverse drug reactions by the companies concerned (article 104 of Directive 2004/27/EC), and also among regulatory agencies (article 105 of Directive 2004/27/EC).

Unrestricted access must be provided to data on adverse drug reactions resulting from spontaneous reports. When no personal data on the patient and/or the reporter are included, issues of confidentiality are not a problem (6). Providing public access to such data has gone smoothly in the Netherlands and the United Kingdom for example (7).

What fate for data collated by EMA? The EMA is not only responsible for ensuring that companies meet their pharmacovigilance obligations for drugs approved through the centralised procedure (article 57f of Regulation (EC) 726/2004); EMA must also centralise European pharmacovigilance data by liaising with national agencies.

For 2005, the EMA annual report states that 49 445 reports of adverse drug reactions were received from Member States, together with 42 120 from other countries and 1150 PSURs (concerning drugs approved through the centralised procedure) (8). In 2005, EMA added a total of 144 786 reports to the EudraVigilance database, of which 73 198 concerned drugs approved through the centralised procedure (8). But patients and healthcare professionals have access to very little of this information (9).

The conditions in which this mass of data is analysed are unclear (especially multiple reports of the same case). EMA should publish periodic reviews of European pharmacovigilance reports.

Information on the reasons underlying drug safety decisions. Article 22 of Regulation (EC) 726/2004 states that the opinions of the European Committee on Medicinal Products for Human Use (CHMP) must be made public; but it does not explicitly mention analyses of pharmacovigilance data, or the discussions underlying opinions and decisions in this field (2). For example, the reasons underlying recent decisions on selective serotonin reuptake inhibitors (SSRI) are inaccessible (4).

However, article 126b of European Directive 2004/27/EC stipulates that: *“Member States shall ensure that the competent authority makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions”* (1). Obligations placed on Member States should also apply to European institutions. And, in the spirit of Regulation (EC) 1049/2001, dealing with public access to documents held by European institutions, the reasons underlying opinions, and the reports on which they are based, must also be made public (10).

Reports of decisions such as those issued by the UK agency (MHRA) are uninformative and must be replaced by documents providing precise arguments. Despite the delay in transposing the relevant text into French law, application of Directive 2004/27/EC by the French regulatory agency gave rise to the first report from the National Pharmacovigilance Committee (11). This may not be much in itself, but this single document clearly illustrates how useful it is for healthcare professionals and patients to understand drug safety decisions, thereby helping to avoid adverse drug reactions. This trend towards greater transparency must continue until openness becomes the rule.

Ending the hypocrisy of commercial confidentiality. Reliable drug consumption data are needed to know the level of population exposure to the risk of adverse drug reactions. This is taken into account by article 23a of Directive 2004/27/EC: *“Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions”* (1). Few regulatory agencies have access to such data, and even less data sorted out by age group or sex (4).

These data have nothing to do with "commercial confidentiality", as mentioned in article 21 of Directive 2004/27/EC with respect to the contents of regulatory agencies' assessment reports that accompany marketing approval decisions. These data have major public health implications and must not be withheld by the authorities, even if drug companies prefer to hide this so called strategic information on their market share (**b**). The number of people exposed to the risk of a particular adverse drug reaction depends directly on sales volumes, and this information is crucial for establishing the risk-benefit balance.

Regulatory agencies and drug companies: end the mix-up!

Drug companies have precise pharmacovigilance obligations. In particular, they must provide agencies all relevant safety data, in a timely and open manner. But companies cannot substitute themselves for an efficient public pharmacovigilance system, and should not be allowed to interfere with either the analysis of drug safety information or the resulting decisions. Companies have too many vested interests to be trusted for managing public health problems.

Exclude companies from the decision-making process. The report to the European Commission notes that companies' pharmacovigilance obligations are only partially enforced: "*the compliance with the expedited procedure is routinely checked by the agencies in only 41% of the cases, compliance regarding PSURs is checked in 56% of the cases; and action in the case of non compliance is only taken in 52% of cases*" (4). These data are in keeping with the results of other studies (12).

The current trend is for drug companies to take over from the regulatory authorities when it comes to analysing and interpreting safety data. In France for instance, companies are present at every step of the process, creating major conflicts of interest (6). The pressure exerted by drug companies, for example by appealing fully justified decisions on purely technical grounds (see the example of appetite suppressants), can delay the decision-making process or even create a state of official inertia that leaves patients exposed to serious adverse reactions to drugs that are in no way essential (13, 14).

The report requested by the European Commission states that decision-making for safety issues is slower for drugs approved through national procedures than for drugs approved through the centralised procedure or by mutual recognition (4). But the report fails to show to what extent differences among Member States dealing with the same drug safety problems are related to the degree of independence from the pharmaceuticals industry.

Private-sector interference in pharmacovigilance decisions must be precisely assessed; and abusive appeals against drug safety decisions must be severely punished.

The place of the ICH. Article 106 of Directive 2004/27/EC states that pharmacovigilance guidelines must be drawn up "*in accordance with internationally agreed formats*", must "*use internationally agreed medical terminology*", and must take into account "*international harmonisation work carried out in the field of pharmacovigilance*" (1). Recognised international institutions clearly have a role to play; this is notably the case of the World Health Organization (WHO), which has a collaborating centre for international drug monitoring.

But the place of the International Conference on Harmonisation for technical requirements of registration of pharmaceuticals for human use (ICH), created jointly in 1990 by regulatory agencies and by the pharmaceuticals industries of the United States, Europe and Japan, appears excessive. Through international conferences and, above all, intensive work by a 14-member committee assisted by industry advisors and administrative experts, but with practically no patient or healthcare professional representation, ICH guidelines have been drawn up and adopted by drug companies and regulatory agencies. In dedicated websites ICH pharmacovigilance guidelines are grouped together under the heading "clinical safety" alongside other guidelines on "efficacy".

Six of these ICH recommendations on pharmacovigilance were adopted by the EMEA Committee on Medicinal Products for Human Use (CHMP) (4). Although they are not legally binding in the EU, these guidelines have major influence and important implications for the organisation of pharmacovigilance, as well as for PSUR content, and the sharing and analysis of data. Thus, the European authorities do not control even the definition of certain elements that are crucial for the interpretation and exchange of pharmacovigilance data.

The authorities thus appear to be beholden to the ICH, and therefore to drug companies, which obviously favour a strict minimum of regulatory obligations when it comes to pharmacovigilance (and drug evaluation). It is crucial to restore the conceptual independence of European pharmacovigilance. Guidelines must

be drawn up by regulatory agencies themselves, after broad public consultations. After all, this is a topic with enormous public health implications.

Publicly funded pharmacovigilance focused on patient safety

By increasing the financial means devoted to European pharmacovigilance, Directive 2004/27/EC offers the chance for a major overhaul of the system.

Guaranteed public funding for pharmacovigilance. Article 102a of Directive 2004/27/EC states that: “*The management of funds intended for activities connected with pharmacovigilance (...) shall be under the permanent control of the competent authorities in order to guarantee their independence*” (1). In the same spirit, article 67.4 of Regulation (EC) 726/2004 stipulates that: “*Activities relating to pharmacovigilance, to the operation of communications networks and to market surveillance shall receive adequate public funding commensurate with the tasks conferred*” (2).

The report requested by the European Commission considers this point to be particularly urgent (4). Indeed, regulatory agencies are currently over-dependent on the fees they receive from drug companies (8,15). These fees and taxes represent more than two-thirds of the funds available to the European and French regulatory agencies (69.2% for EMEA in 2005 and 73.5% for French agency in 2004) (8, 15). And this financial dependency is one of the elements that undermine these agencies’ impartiality in matters of pharmacovigilance.

Public funding provided for by European legislation must be sufficient to end this dependency at the centralised level. And Member States should do the same nationally.

No “subcontracting” of pharmacovigilance information to drug companies. Usually, “Dear Doctor” letters that announce changes in summaries of product characteristics for safety reasons are addressed by the companies concerned. It would clarify matters if these letters were sent out by regulatory agencies, as this would place the accent on public health rather than on the special interests of the pharmaceuticals industry.

The distribution of Dear Doctor letters by drug companies creates a risk of abuses. Take the celecoxib scandal for example: the French medicines agency had to forbid – after it had been sent out – a company “information letter” on celecoxib which, instead of providing the necessary warnings, was in effect a disguised advertisement, claiming that celecoxib was safer than rofecoxib, a similar drug that had already been taken off the market (16).

The European legislation should provide for sufficient funding so that regulatory agencies have the means necessary to distribute pharmacovigilance information themselves.

Public collection of adverse drug reaction reports. The European legislation requires that drug companies assume the bulk of responsibility for the adverse drug reactions of their products. As such, it is normal that companies collect data on adverse drug reactions. But these data are also of interest to patients, healthcare professionals and the scientific community as a whole. Private-sector pharmacovigilance must not be allowed to substitute for publicly funded pharmacovigilance systems.

At the time of writing, EMEA is still unable to collect reports of adverse drug reactions directly from healthcare professionals. And other public bodies, such as regional pharmacovigilance centres, must also be in a position to collect such reports, as proposed by the report to the European Commission (4).

The European legislation should provide enough funds to ensure the efficient functioning of such a collection system.

Reporting by patients is needed. Article 22 of Regulation 726/2004/EC simply states that “*patients shall be encouraged to communicate any adverse reaction to healthcare professionals*” (2). Yet direct reporting by patients increases the sensitivity of pharmacovigilance systems, as shown by the example of selective serotonin reuptake inhibitors (SSRI) and by a study assessing the sources of decisive information on adverse drug reactions in children (17,18).

Various EU Member States already collect reports directly from patients, including Denmark, the Netherlands (LAREB), and the United Kingdom (MHRA yellowcard system) (c)(19). Independent organisations also collect this information, in the Netherlands (DGV), Sweden (Kilen), and Germany (Netzwerk ATI) for example (19). With the growing number of drug safety scandals, accepting the principle of direct reporting by patients would help to restore public confidence.

The European legislation should provide sufficient funds to ensure that patients are listened to and informed.

Clarifying the impact of pharmacovigilance on approval conditions. Regulatory agencies themselves, and the report to the European Commission, recognise that pharmacovigilance decisions are taken too slowly, especially for drugs approved through national procedures (4).

Opinions of pharmacovigilance bodies are non binding, whatever the marketing approval procedure. Moreover, guidelines published in 2005 by the European Commission, defining “*serious risks to public health*” that justify terminating the mutual recognition procedure, are extremely flimsy, and therefore place patients at a risk of adverse reactions to drugs that have no demonstrated therapeutic advantages (20).

A report on the US Food and Drug Administration (FDA) states that failures in postmarketing follow-up are largely due to fact that the Office of Drug Safety lacks sufficient clout in the postmarketing decision-making process, which is under the authority of the drug licensing body (Office of New Drugs) (21).

In Europe, pharmacovigilance must be taken out of the hands of the toothless Pharmacovigilance Working Party (PhVWP) of the CHMP. Instead, a European Pharmacovigilance Committee should be created, whose opinions (fully justified in the same way as CHMP opinions) would be a sufficient basis for the authorities to withdraw or modify a marketing approval (without the need for a CHMP opinion). Same thing at the national level: in France for example, the pharmacovigilance committee should no longer have to ask the drug approval authority to re-assess a drug’s risk-benefit balance when seeking to modify the marketing approval.

Postmarketing studies. The European legislation only provides a legal basis for pharmacovigilance surveys and follow-up studies during the first 5 years for drugs approved through the centralised procedure, and only in “*target groups of patients*” (articles 26 and 57 of Regulation 726/2004/EC) (2). But often, pharmacovigilance and follow-up studies that are a condition for marketing approval are not completed in the agreed timespan (sometimes they are not done at all) (d).

These obligations must be strictly enforced. If the company fails to conduct such studies, then the product concerned should be immediately withdrawn from the market and a fine at least equivalent to the sales figures generated during the period concerned should be imposed.

Furthermore, when required by emerging safety problems (signals), independent pharmacovigilance studies should be undertaken without delay by the health authorities, financed by public funds specially set aside to deal with such events.

Proactive management of the risk of adverse drug reactions. The European legislation does not mention special monitoring of certain drugs (e). Nevertheless, such lists are established and regularly updated in some countries such as the UK (an inverted black triangle is printed on the labels of new drugs and vaccines), Sweden, New Zealand (Intensive Medicines Monitoring Programme (IMMP)) (22,23).

This has the advantage of encouraging reports and accelerates the collection of pharmacovigilance data. And the risk of over-reporting appears to be manageable in countries with experience of such lists. EMEA should compile a list of drugs requiring special pharmacovigilance follow-up in Europe.

Evaluating the impact of pharmacovigilance decisions. The report to the European Commission states that the impact of pharmacovigilance decisions is regularly assessed by only 4 of the 29 agencies surveyed (4). This recalls regulatory agencies' failure to enforce companies' pharmacovigilance obligations. Published studies are rare (24).

Routine assessment of the efficacy of pharmacovigilance measures, particularly during crises, requires public funding as provided for in the European legislation.

Pharmacovigilance systems must offer the same guarantees to all European citizens, however a drug is approved or marketed. The new legislation offers the possibility to improve pharmacovigilance in Europe: it must therefore be applied rigorously and without delay, and be improved where necessary.

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a- Accordingly to Regulation (EC) 1049/2001 on access to documents held by European institutions, PSURs should be made public because they are "Commission documents " once they enter EMEA (ref 10). Obliging European citizens to make special requests for this information introduces unnecessary delays.

b- The rules of procedure of the French pharmacovigilance committee defines as confidential "all information of a commercial and industrial nature, such as manufacturing processes, research and development, financial and economic information, and commercial strategies" (ref 25).

c- The French Agency, through task forces including patient associations, consumers and French Agency representatives, has developed a standard form for reporting adverse events by patients, and a user guide (ref 26).

d- See for example the repeated delays in the publication of the French Cadeus study report (refs 27,28); and American experience in this area (ref 21). The Commission's regulation dealing with conditional marketing authorisation, published in 2006, is not particularly reassuring in this regard (ref 29).

e- According to article 123.4 of Directive 2004/27/EC, EMEA is only obliged to keep "a publicly accessible register of medicinal products authorised (...) Member States shall notify the Commission if any medicinal products is authorised or ceases to be authorised". EMEA is not required to give its reasons for suspending marketing approval (ref 1).

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Mobilising European citizens concerned with drug safety

The European Directive and Regulation on human medicines, published in the Official Journal of the European Union on 30 April 2004, was adopted through a codecision procedure involving the European Parliament and the Council of Ministers (1-3). Patients, consumers, healthcare professionals and insurance organisations mobilised, notably within the Medicines in Europe Forum, in order to participate in the debates that lasted more than two years, from late 2001 to early 2004 (3).

Thus, regarding pharmacovigilance, European Regulation (EC) 726/2004 aims to "put in place stringent and efficient pharmacovigilance procedures, to allow the competent authority to take provisional emergency measures, including the introduction of amendments to the marketing authorisation and, finally, to permit a reassessment to be made at any time of the risk-benefit balance of a medicinal product." (preamble 30) (2). It also aims to allow "intensive supervision of undesirable effects (...) so as to ensure the rapid withdrawal from the market of any medicinal product presenting a negative risk-benefit balance under normal

conditions of use” (preamble 29) (2). And European Directive 2004/27/EC underlines the need to strengthen “Pharmacovigilance and, more generally, market surveillance and sanctions in the event of failure to comply with the provision” (preamble 20) (1).

Citizens in some European countries have since become even more alert to the guarantees offered by Member States and regulatory agencies on pharmacovigilance issues. For example, an Irish petition demanded the creation of an independent pharmacovigilance body in Ireland (ref 4). Some common-sense decisions on pharmacovigilance have been taken at the national level, such as greater access to pharmacovigilance data in the Netherlands and the United Kingdom (refs 5,6).

However, the Medicines in Europe Forum failed in its attempt to improve the new European regulation with respect to direct reporting of adverse events by patients themselves. Thus, article 101 of Directive 2004/27/EC does not even mention this issue (1).

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