



Brussels, October 2009
Joint analysis

Pharmacovigilance in Europe: the European Commission's proposals endanger the population

Summary

- **A series of public health disasters (from thalidomide in the 1960s to rofecoxib (Vioxx^o) at the beginning of this century) have served to remind us of the crucial nature of pharmacovigilance. To this end, the European Commission's proposed legislative changes represent a serious regression in the protection of European citizens.**
- **Among the key issues of concern:**
 - **the spread of weak marketing authorisation practices, justified by post-authorisation safety studies and 'risk management' programmes that would allow inadequately evaluated medicines to reach the market;**
 - **the withholding of adverse drug reactions data, the collection and interpretation of which are abandoned to pharmaceutical companies, despite the fact that these companies have a vested interest in delaying pharmacovigilance decisions;**
 - **the increased financial and intellectual dependency of health authorities on pharmaceutical companies (due to the end of public funding obligation for pharmacovigilance activities, and to the hierarchical dependency of pharmacovigilance authorities on marketing authorisation committees), which leads to an opaque and increasingly biased decision-making process.**
- **Member States are responsible for the protection of their populations. They cannot accept the exposure of their populations to adverse drug reactions from medicines that have been marketed prematurely. Neither should they support the delegation of tasks that are the responsibility of public pharmacovigilance systems to pharmaceutical companies.**
- **The EU Commission proposals on pharmacovigilance can still be refocused in defence of public interest, provided they are profoundly amended in order to end to the conflation of roles (read our 15 concrete recommendations on page 6).**

Adverse drug reactions are responsible for at least 5% of hospital admissions and are the 5th ranking cause of hospital deaths according to the European Commission itself¹. Many countries developed public pharmacovigilance systems in the aftermath of disasters such as *thalidomide* in the 1960s, in which tens of thousands of women who took this sedative drug during pregnancy gave birth to severely handicapped children due to atrophy of one or more limbs (a).

In spite of the under-reporting of adverse effects by healthcare professionals (b), these national and regional centres manage to identify signals and alerts, helping national authorities take the necessary decisions to protect their citizens: adding special warnings to the prescribing information and package leaflet; or

a- Many Member States have set up regional pharmacovigilance centres (France, Italy, the Netherlands, Poland, Portugal, Spain, the United Kingdom). Countries with smaller populations tend to have only national pharmacovigilance centres, often within their drug regulatory agencies (for example Belgium, Croatia, Estonia, Greece and Luxembourg). Germany has several centres, some specialising in a particular type of adverse effect (for example, the centre for the documentation of serious cutaneous reactions).

b- Several countries also collect reports submitted by patients: the United Kingdom (the yellow card scheme), the Netherlands, Denmark, Belgium, France. In addition, many studies have shown that it is perfectly possible to boost the reporting rate by healthcare professionals by offering real support for this activity, which is currently unacknowledged and undervalued.

suspending a drug's marketing authorisation or even withdrawing it from the market. It is therefore vitally important that the expertise of these centres is maintained and developed.

In the current context of innovation failure, in line with an understandable industrial logic, pharmaceutical companies seek to **prolong the marketing period during which their new drugs are patent-protected and maximise the return on their investment**, for example through:

- increasingly premature marketing authorisation (which, from the point of view of the pharmaceutical companies, has the added advantage of minimising research costs associated with the evaluation of new drugs);
- keeping their drugs on the market for as long as possible, if necessary by withholding data about their adverse effects (see below).

In December 2008, the European Commission published some proposals regarding pharmacovigilance. These proposals would only aggravate the current situation and represent a major step backwards in terms of protecting the European population, particularly by disrupting European pharmacovigilance¹.

In this document, we present 3 major reasons to amend these proposals (pages 1 to 5), then propose concrete recommendations (pages 6 to 11).

3 major reasons to amend the European Commission's proposals

"Risk management plans" and other post-authorisation studies are deceptive Pharmaceutical companies use them to market inadequately evaluated medicines prematurely

Since 1965 in Europe, the conditions for obtaining marketing authorisations are demonstration of the drug's efficacy, safety and quality. Efficacy is usually demonstrated by conducting clinical trials in which the effects of the new drug are compared to the effects of a placebo. Some marketed drugs constitute a step backwards, exposing patients unnecessarily to adverse effects when other safer treatments already exist for the same indications. This was the case for *rofecoxib* (formerly marketed under the brand name Vioxx^o), an anti-inflammatory agent that was marketed even though it was no more effective than *ibuprofen* but exposed patients to more risks. In 2004, after having been marketed for several years, it was withdrawn when independent teams of scientists demonstrated tens of thousands of adverse cardiovascular reactions, some of which were fatal (particularly myocardial infarction)².

Moreover, experience acquired over recent years shows that the use of "risk management systems" (RMSs) is not such a good idea after all: it is counterproductive in terms of public health. RMSs are too often used to reassure the public when inadequately evaluated drugs have been granted premature marketing authorisation. The examples of *rimonabant* (formerly marketed as Acomplia^o) and *varenicline* (Chantix^o) illustrate this point (c).

Rather than proposing to make the pre-authorisation evaluation of new medicines more thorough, the European Commission is planning:

- more widespread use of RMSs (*proposed articles 104(3)c and 104a of the Directive, and proposed article 21 of the Regulation*), possibly accompanied by post-authorisation studies (*proposed article 22a of the Directive and article 10a of the Regulation*);
- promoting "conditional" marketing authorisation for inadequately evaluated medicines without it being justified by a public health need (*proposed article 21a of the Directive*) (d).

According to the European Commission's Directorate General for Enterprise, the aim of these RMSs and post-authorisation studies is to open the way for "*earlier product authorisation [which] provides faster return*

c- *Rimonabant* (formerly marketed as Acomplia^o) was licensed for the treatment of obesity. But one of its effects is to increase the number of suicides. The European agencies' response was initially confined to setting up a "risk management system", none of the details of which were made public. It took about 2 years after its marketing authorisation was granted for *rimonabant* to be withdrawn from the market! The US Food and Drug Administration had refused to approve this drug from the outset. Similarly, *varenicline* (Chantix^o) has an unfavourable risk-benefit balance in smoking cessation (psychiatric disorders including increased suicide risk, etc.), but for now the only measure has been to operate a risk management system.

d- For patients with no further treatment options (multidrug-resistant HIV, incurable cancers or where available treatments provide mediocre results, etc.), there are already provisions at the European level and Member State level to accelerate access to drugs: conditional marketing authorisation (*article 14.7 of Regulation (EC) 726/2004*), marketing authorisation granted for exceptional circumstances (*article 22 of Directive 2001/83 EC (consolidated) and article 14(8) of Regulation (EC) 726/2004*), accelerated marketing authorisation (*article 14(9) of Regulation (EC) 726/2004*); in France, 'temporary authorisations' (ATU), and 'temporary treatment protocols' for off-label use in a hospital setting, etc.

on investment and, by reducing the cost of capital [through increased investor confidence], the total cost of product development is reduced"³.

Yet it has been demonstrated that premature licensing is achieved at the expense of proper evaluation, leading to more pharmacovigilance issues further down the line⁴. And years of experience show that, in Europe, the US and Canada, pharmaceutical companies generally do not honour their commitments on post-authorisation evaluation^{5,6}. Worse still, post-authorisation studies are too often used as a pretext to market a drug with an unfavourable risk-benefit balance for a few more years, while awaiting the results of the study (c). And, in the current context, where direct-to-patient communication by pharmaceutical companies is being deregulated (proliferation of "disease management" or "compliance support" programmes financed by pharmaceutical companies), it is essential that risk management systems and post-authorisation studies are not used to foster patient loyalty to a particular brand of a medicine⁷.

See our concrete recommendations for improving the European Commission's proposals, on pages 6 and 7 (recommendations Nos. 1, 2, 3 and 4).

Shifting "responsibilities" to pharmaceutical companies and "centralising" pharmacovigilance data are just wishful thinking

The reality is the withholding of data on adverse drug reactions

The Member States' national and regional pharmacovigilance centres rely on the expertise of teams specialised in pharmacology and on their proximity to the population (e). The collection of adverse events reports is a critical step in enabling subsequent analysis and reliable interpretation of the data.

Rather than proposing to develop this public expertise or extend it to the other Member States, the European Commission intends to construct an organisation that will deprive the specialised teams from these pharmacovigilance systems of data:

- Member States will be able to ask health professionals to report adverse effects directly and solely to pharmaceutical companies (*proposed article 102(1)*);
- pharmaceutical companies will also be able to receive reports from health professionals and patients (*proposed article 107(1) and (2) of the Directive*);
- and the pharmaceutical companies will be responsible for recording these reports at "a single point within the Community" (the Eudravigilance database) (*proposed article 107(1) of the Directive*) (f).

And yet, more than 5 years after its creation, the Eudravigilance database is still not operational: the national regulatory authorities cannot use it effectively and denounce an approach that will result in a "levelling down" phenomenon⁸. Furthermore, imposing International Conference on Harmonisation (ICH) standards on the data entered into the Eudravigilance database risks stripping them of all clinical significance (*proposed articles 101(4) and 108 of the Directive*) (g).

This arrangement provides an opportunity for pharmaceutical companies to withhold and manipulate the data. Many recent examples serve as reminders that the pharmaceutical companies' sense of responsibility is often overcome by the enticement to withhold data or delay its disclosure, so as to delay decisions that would adversely affect sales (h).

e- This proximity, in terms of language and knowledge of local lifestyle, enables easy contact with reporters, usually by telephone. Teams can therefore obtain any additional information that might be required to analyse the data. Without this step the information contained in the report could be lost. Incomplete reports simply cannot be analysed.

f- The European Commission is also proposing that the periodic safety update reports (PSURs) prepared by pharmaceutical companies need no longer show a detailed listing of the various individual cases reported (ref. 1), thus removing the last means available to the authorities for monitoring the pharmaceutical companies' activities (ref. 17).

g- The ICH is an entity composed of representatives from pharmaceutical companies and drug regulatory agencies which guides drug policy by producing "recommendations" and "guidelines". The ICH developed the MedDRA^o dictionary (Medical Dictionary for Regulatory Activities Terminology), which is supposed to standardise adverse effect reporting. In practice, it requires encoding adverse effects by "symptom" using the "lowest level term", at the risk of losing their clinical significance. This risk is particularly high since this "symptom" must be linked to one or more "categories" (system organ class, SOC): the data from one patient is therefore spread across several "categories" making the evaluation of cases difficult (ref.18). Furthermore, some effects can be made to "disappear" by linking them to the wrong categories. For example, if the symptom "weight gain of 20 kg" is encoded in the "investigations" category, where nobody would think of looking for it, this adverse effect will be concealed.

h- For example, in 2000, data from the Vigor trial revealed an increased rate of infarction in patients taking *rofecoxib* (ref. 2). Merck then put forward the hypothesis that the comparator drug used in this trial had a beneficial cardiovascular effect. In the time that passed between the first results and market withdrawal of the drug, four years, tens of thousands of cardiovascular events occurred that

Moreover, centralising all reporting at the European level without any regional or national analysis will dilute and alter the data, hindering detailed analysis and interpretation, and finally making the Eudravigilance database inefficient or completely useless.

In summary, the European Commission's proposals unearth dangerous opportunities for pharmaceutical companies to bypass the Member States' public pharmacovigilance systems, then gradually replace them, and lead to their demise in the medium term by asphyxia, by depriving them of data.

See our concrete recommendations for improving the European Commission's proposals, on pages 7 and 8 (recommendations Nos. 5, 6, 7 and 8).

The financial and intellectual dependence of regulatory authorities on pharmaceutical companies leads to increasing bias in the decision-making process, which still lacks transparency

In recent years, several major pharmacovigilance scandals have raised questions about the ability of regulatory authorities to protect European citizens effectively (i). Decisions about the measures to be taken are reached slowly and after much prevarication, particularly due to the fact that the preparatory phase of the decision-making process, i.e. data interpretation, is entrusted to the pharmaceutical companies. Indeed, it is up to the pharmaceutical companies (even though they are both the judges and the judged) to produce the "*scientific evaluation of the risk-benefit balance*" of their drug within the framework of the periodic safety update reports (PSURs).

The pharmaceutical companies' stronghold over data interpretation is still partially counteracted by the proactive work of the specialised pharmacovigilance teams that manage to identify signals by analysing the well-documented cases to which they have access (see above). But as the recommendations of the pharmacovigilance committees are non-binding, drug licensing committees do not take them sufficiently into account to amend or revoke marketing authorisation (j). Indeed, the licensing committees have two types of conflicting interests with regard to pharmaceutical companies:

- an intrinsic conflict of interest: having licensed the implicated medicine in the first place, experience shows that they find it difficult to raise doubts about their original decision (k);
- and a financial conflict of interest, since they are now funded almost exclusively by pharmaceutical companies, through the fees the companies pay (l).

The regulations introduced in 2004 increased the independence of and resources allotted to pharmacovigilance by requiring its public funding: "*activities relating to pharmacovigilance (...) shall receive*

were attributable to *rofecoxib* (Vioxx[°]), some of which were fatal (ref 19). In another example from 2007, Lilly gave several tens of thousands of dollars in compensation to each of the 28 000 plaintiffs in the US who accused it of not having informed them honestly of the adverse effects of the neuroleptic drug *olanzapine* (Zyprexa[°]), which causes diabetes and significant metabolic disorders, a fact which was known to the company (ref. 20). In a further example pharmacovigilance data on *paroxetine* (Deroxat[°]/Seroxat[°]) in children was shown to have been withheld (increased suicide risk) (ref. 21).

i- Examples from the last decade include the scandals involving *rofecoxib* (Vioxx[°]) with fatal cardiac events, so-called selective serotonin reuptake inhibitor antidepressants and *rimonabant* (formerly marketed as *Acomplia*[°]) with increased suicide risk, *olanzapine* (Zyprexa[°]) with diabetes and metabolic disorders, and *rosiglitazone* (Avandia[°]) with fatal cardiac disorders, etc.

j- At the European level, these licensing committees are the Committee for Medicinal Products for Human Use (CHMP) for centralised marketing authorisation procedures, and the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh) for decentralised or mutual recognition marketing authorisation procedures.

k Examples include:

- the case of *nimesulide*: after several months of prevarication, the CHMP confirmed the hepatic risks of *nimesulide* (Nexen[°]), but it contented itself with half-measures, notably limiting the treatment duration to 15 days, leaving European patients exposed to a risk of death that was unjustified, given the large number of existing anti-inflammatory drugs with similar efficacy but which are less dangerous;

- the case of *rimonabant* (Acomplia[°]): *rimonabant* (Acomplia[°]) was withdrawn from the European market in October 2008, only 2 years after being granted marketing authorisation in obesity, due to an unfavourable risk-benefit balance (increased suicide risk). The US drug regulatory agency (FDA) on the other hand had refused to approve *rimonabant* on the basis that the risks were inadequately elucidated);

- the arbitration procedure on the combination *paracetamol + dextropropoxyphene* (Di-antalvic[°]): this arbitration went on for a year and a half before the drug was finally withdrawn from the market in June 2009 due to its unfavourable risk-benefit balance.

l 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 pharmaceutical companies, which represents 74% of its revenue (and this percentage is constantly increasing) (ref. And many of the experts consulted by the drug regulatory agencies are also often working for pharmaceutical companies (ref. 23).

adequate public funding commensurate with the tasks conferred" (article 67(4) of Regulation (EC) 726/2004). However the European Commission's proposals go against the spirit of this progress, by ending the requirement for public funding at both a national and community level. It proposes that pharmacovigilance may be financed by the fees paid by the pharmaceutical industry, making the funding of pharmacovigilance directly dependent on the volume of marketing authorisation activity carried out by the regulatory agencies (proposed article 105 of the Directive and proposed amendment of article 67 of the Regulation). The funding of pharmacovigilance by pharmaceutical companies conflicts, however, with the advantage to pharmaceutical companies of delaying the disclosure of pharmacovigilance data.

Rather than increasing the intellectual independence of the regulatory authorities from the pharmaceutical industry, the European Commission proposals continue to allow the pharmaceutical companies free rein to decide whether they consider the risk-benefit balance of their drugs has changed, since the company still produces the assessment to be included in the periodic safety update report (PSUR). Furthermore, the Commission proposes that Member States may hand over the "follow up of such reports" to pharmaceutical companies (proposed article 107(4) of the Directive). The Commission's proposals also require the submission of one PSUR for the entire Community, at a frequency that is "appropriate" to the drug's risk profile (proposed article 107c(6)c of the Directive). Consequently, 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) (proposed article 107b(3) of the Directive). And yet there are dramatic examples of belatedly identified adverse effects, even 30 years after obtaining marketing authorisation (m).

Rather than proposals that strengthening the hierarchical and therefore intellectual independence of the pharmacovigilance authorities (regional and/or national systems, often organised into pharmacovigilance committees within drug regulatory agencies) from the licensing committees, the European Commission is planning an organisation based on:

- broadening the remit of the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) to cover pharmacovigilance issues;
- setting up a Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) that is not big enough, has neither authority nor autonomy, and the role of which will still be limited to issuing "recommendations" (proposed amendment of article 27 of the Directive and article 56(1)(aa) of the Regulation).

In this setup, the licensing committees (CHMP or CMDh) make proposals to the European Commission on whether to maintain, amend or suspend marketing authorisations, even when these decisions relate to pharmacovigilance issues, and they are not required to apply the PRAAC's recommendations.

Finally, the lack of transparency surrounding pharmacovigilance data is maintained at each stage of the decision-making process, on the pretext that the data are "commercially confidential". The creation of minimalist web portals by Member States (proposed article 106 of the Directive) and the renewed promise of "appropriate levels of access" to the Eudravilance database for the public (article 102 of the Directive 2001/83/EC (consolidated) and article 57 of Regulation (EC) 726/2004) are not sufficient to ensure public access to pharmacovigilance data. For example, there is no proposal to make PSURs, or even the regulatory authorities' assessment reports of these PSURs, public. Yet Regulation (EC) 1049/2001, on public access to documents from European institutions, stipulates that these documents should already be publicly accessible^{9,10}. Furthermore, it is proposed that only the summaries of the Committee meetings will be made available to the public, and not those of the Agencies' working parties or the CMDh (proposed article 26 of the Regulation) (n). Within this scenario, how is it possible to trust the authorities' decisions and the rationale behind them?

See our concrete recommendations for improving the European Commission's proposals, on pages 8 and 11 (recommendations Nos. 9, 10, 11, 12, 13, 14 and 15).

m- For example:

- the combination *dextropropoxyphene + paracetamol*: the EMEA recommended its withdrawal throughout Europe in June 2009, whereas it was originally granted marketing authorisation in Europe in the 1960s (ref. 24);
- *diethylstilbestrol* (DES)), which causes uterine cancer and malformations in women exposed to this drug in utero while their mothers were pregnant, the adverse effects of which were recognised 30 years later (ref. 25);
- wall germander, a medicinal plant traditionally used for decades, but which has been shown to be hepatotoxic (ref. 26); etc.

n- Yet article 126b of Directive 2001/83/EC (consolidated) concerning the transparency obligations of authorities, stipulates that the competent authority must "make publicly accessible (...) records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions!"

Each stakeholder has a distinct role to play: our concrete recommendations

The human and financial costs of the adverse effects of drugs are very high, and are borne by the patients who experience them and by society. Yet instead of strengthening pharmacovigilance in Europe, the European Commission's proposals will pave the way for a major decline in the protection of the European population.

Member States have a responsibility to protect their populations. They should not agree to expose their citizens to the adverse effects of drugs that have been released onto the market prematurely. Neither should they agree to their public pharmacovigilance systems outsourcing tasks that clearly fall under the scope of public health to the pharmaceutical industry, which least wants pharmacovigilance signals to come to light.

Provided that the Commission's proposals are profoundly amended, they can be refocused to defend the public interest. Our concrete recommendations on how to achieve this are grouped by theme.

Marketing authorisation

Recommendation 1:

- **Require demonstration of therapeutic advance in order to obtain marketing authorisation.** This should be the criterion, rather than "efficacy", for a company to obtain a marketing authorisation. Demonstrating that a new drug offers a real therapeutic advance requires comparative clinical trials to show that it is more effective or less dangerous than the standard treatment. It is also an effective way of shifting the emphasis of research to neglected diseases, thereby enabling the pharmaceutical industry to be truly innovative¹¹.

Recommendation 2:

- **Maintain the significance of marketing authorisation in terms of public health protection.** It is essential that drugs are evaluated properly before being granted marketing authorisation, to avoid the entire European population being used as "guinea-pigs", potentially subjected to adverse effects that were undetected or underestimated prior to marketing. If no genuine public health need justifies it, the granting of hasty, cheap-rate marketing authorisations, behind a smokescreen of "risk management systems" and other post-authorisation studies, must be refused. **"Conditional" MAs must remain the exception rather than the rule, and should be reserved for the accelerated approval of drugs that fulfil an important unmet public health need.**

Risk management systems and post-authorisation studies

Recommendation 3:

- **Use "risk management systems" to strengthen pharmacovigilance.** "Risk management systems" should be used in addition to standard pharmacovigilance for any medicine where doubts about adverse effects exist or emerge, even for medicines that have been in use for a long time. Risk management systems must be designed and conducted under the close supervision of health authorities (national and regional pharmacovigilance systems in particular), with complete independence. Their objectives must be to identify all the adverse reactions of the drug in question, to clarify their frequency and seriousness, both short-term and long-term, and above all to prevent their recurrence by helping the regulatory authorities to reach a timely decision.

Recommendation 4:

- **Help patients identify new drugs that have been marketed prematurely and are "under intensive monitoring".** A special warning should appear on the package leaflet, inviting patients to report any adverse effects to the appropriate authorities, and all secondary packaging (box) and immediate packaging (for example the blister pack) should be labelled with a black triangle pointing downwards (▼) next to the brand name. This pictogram is already widely used in the European Union and its wider use should help to contribute to more judicious use of these drugs.

Collection of pharmacovigilance data and the Eudravigilance database

Recommendation 5:

- **Maintain and significantly develop the expertise of public pharmacovigilance systems.** There is more to pharmacovigilance than simply recording adverse event reports. The focus of the European Commission's proposals must be shifted so that existing pharmacovigilance systems are consolidated. Adequate public funding must provide them with the resources to conduct independent, high-quality, expert analysis, and to fully engage in proactive pharmacovigilance (see recommendation 11 below).

Recommendation 6:

● **Encourage patients to report adverse events directly to the regulatory authorities.** Authorising patients to report adverse effects directly to the regulatory authorities through a national drug safety web portal is a welcome measure, but it is insufficient. The system excludes certain categories of the population, such as people who do not know how to use computers or the Internet, and immediate contact with specialised pharmacovigilance teams is lacking, so initial reports cannot be expanded (*proposed article 107a*). To encourage direct reporting by patients:

- the box of all drugs should contain a reporting form, at least for the first 2 years after marketing authorisation was granted, giving the precise details of the pharmacovigilance centre to which the patient should send the report (o);
- patient reporting should be possible by telephone, fax or email (the FDA and the UK already operates like this).

Recommendation 7:

● **Ensure the quality of the content of the Eudravigilance database.** Reports from patients, healthcare professionals or pharmaceutical companies must be collected and centralised by each Member State's independent pharmacovigilance system. These independent pharmacovigilance systems will be able to add valuable information based on their particular expertise and will then be responsible for sending the data to the Eudravigilance database. By **requiring that reporting operates through each Member State's pharmacovigilance system** the quality of the content of the Eudravigilance database can be ensured (p). This requirement must also enable the competent authorities of Member States to:

- have a clear understanding of the adverse effects occurring in their country;
- be able to update their national database;
- make this information accessible to their country's population in its own language.

As for adverse effects caused by medication errors, reports must be collected and centralised by programmes for the reporting and prevention of medication errors, which exist in many Member States¹². Such non-punitive programmes can analyse the series of events that resulted in the medication error. These programmes can add valuable information based on their particular expertise, and are then responsible for sending the data to the Eudravigilance database (q).

Recommendation 8:

● **Enable more effective sharing of data about adverse effects: transparency of databases, user-friendly package leaflets.** Data about the adverse effects experienced by patients are not commercial data to be collected by pharmaceutical companies as part of their marketing services¹⁰. They are public scientific data. They need to be analysed and interpreted to prevent recurrence and lead to independent decision-making. The Eudravigilance database must enable national regulatory authorities to share their data with other Member States and with the public, who must be able to access its full content in a usable format (*proposed article 107a (2 of the Directive)*). The US Food and Drug Administration (FDA) already provides this type of information through quarterly data extracts from its Adverse Event Reporting System (AERS) database¹³, as does the national pharmacovigilance centre of the Netherlands¹⁴.

Studies show that patients read package leaflets, but struggle with the complex language used (medical jargon) and poor visual presentation¹⁵. Better quality, more user-friendly package leaflets, developed through test consultations with patients (*in accordance with article 59 of the Directive 2001/83/EC (consolidated)*) would appear more useful than a vague "*summary of data relevant to the benefits and risks of the medicinal product*" (*proposed article 107b*).

o- For Member States with regional centres, a telephone or fax number should be provided or an email template with a part that will vary according to the region.

p- The Eudravigilance database cannot replace the local network currently composed of national public pharmacovigilance systems. Local networks must be the entry point for data if we are to benefit from their expertise and their proximity to the population.

q- Local Medication errors often occur following a series of events or multifactorial causes. The recording of medication errors in the Eudravigilance database therefore requires the provision of fields that will enable data to be entered about each stage of drug supply as well as the error taxonomy (ref 27).

Interpretation of pharmacovigilance data and PSURs

Recommendation 9:

• **Objective decision-making, based on independent analysis taking all the available data into account.** The role of the regulatory authorities should not be limited to the evaluation of the data provided by the pharmaceutical companies alone (in PSURs) (*proposed article 107d and 107e of the Directive*), which could bias their conclusions. Scientific assessment of the risk-benefit balance of drugs requires all the available data to be considered:

- periodic safety update reports provided by pharmaceutical companies (including the list of properly documented reported cases);
- data from health professionals' and patients' reports provided by the pharmacovigilance systems of the various Member States;
- data published in the literature;
- data from clinical trials and post-authorisation studies.

This assessment must be entrusted to the Member State's competent authorities responsible for pharmacovigilance, acting as a rapporteur. They will be able to call on the services of working parties composed of experts who are independent of both the pharmaceutical companies and the licensing committees, with complete transparency. A single assessment ought to be possible for drugs authorised in more than one Member State and made public, for example, within 6 months of the company submitting the periodic safety update report (PSUR).

Recommendation 10:

• **Continue regular surveillance of drugs considered to have been in "well-established medicinal use".** Periodic safety update reports (PSURs) need to be submitted regularly and at least every 5 years for so-called "well-established" medicines.

Independence of the decision process and the role of the European pharmacovigilance committee (PRAAC)

Recommendation 11:

• **Maintain public funding for pharmacovigilance in recognition of its public interest.** Public authorities are responsible for monitoring and identifying adverse effects: because they are accountable with respect to public health; because they have assumed responsibility for granting marketing authorisations. The requirement for public funding of pharmacovigilance, which is a public health activity, must be maintained (*in accordance with Article 67.4 of the Regulation (EC) 726/2004*). This public funding must be considered as an investment for society, particularly considering the savings to be made: a decrease in adverse drug reactions means a reduction in hospitalisations, suffering, deaths, days of sick leave, and medical consultations.

Recommendation 12:

• **Ensure the independence of European pharmacovigilance from the licensing committees.** Entrusting the management of pharmacovigilance issues to the licensing committees amounts to depriving the system of the expertise of the teams specialised in pharmacology, which are able to objectively assess the causality of adverse events. To ensure independence, competence and timely decision-making in pharmacovigilance, we propose clearly separating the powers between:

- the licensing committees, which would be responsible for evaluating drugs prior to marketing authorisation and for post-authorisation variations (unless pharmacovigilance issues have been raised);
- the pharmacovigilance systems of the Member States, which would be responsible for the surveillance of adverse drug events and for proposing the measures to be taken for all pharmacovigilance issues.

The clarification of roles was one of the main recommendations made by the Institute of Medicine in its 2006 report to improve pharmacovigilance operations within the US Food and Drug Administration (FDA)¹⁶.

Just as there is a European licensing committee for centralised marketing authorisations (CHMP) and a Co-ordination Group for mutual recognition or decentralised marketing authorisations (CMDh), we propose organising pharmacovigilance around:

- a European pharmacovigilance committee, equivalent to the CHMP in terms of authority (see recommendation 13 below), responsible for pharmacovigilance-related post-authorisation evaluation for drugs approved through the centralised procedure;
- and a "pharmacovigilance risk assessment coordination group", responsible for pharmacovigilance-related post-authorisation evaluation for drugs approved through the decentralised procedure or by mutual recognition. This coordination group must enable effective cooperation between Member States. It must consist of independent experts, with no conflicts of interest, competence in pharmacovigilance, and be

hierarchically independent of the national licensing committees. The agenda and detailed minutes of its meetings must be made public.

Recommendation 13:

● **Strengthen the authority and increase the resources of the European pharmacovigilance committee (PRAAC).** The PRAAC advisory committee should be renamed the "European pharmacovigilance committee". It must have similar powers to the CHMP. After analysis and discussions of Member States' assessments performed under its supervision (rapporteur and co-rapporteur systems), the European pharmacovigilance committee must be able to propose decisions directly to the European Commission (namely pertaining to withdrawals or changes to marketing authorisations), free of any influence from the CHMP or CMDh. The European pharmacovigilance committee must be sufficiently autonomous and have enough resources to carry out any research it deems necessary to protect the European population (proactive pharmacovigilance).

It must be entirely financed by public funds. Its resources need to be increased to at least one representative and one deputy member per Member State (like the CHMP); its members should not have any conflicts of interest through links with pharmaceutical companies and it must be hierarchically independent from the national drug licensing committees. Meeting transcripts must be made public, including voting details.

Similarly, the "pharmacovigilance risk assessment coordination group" should have similar powers with regards to marketing authorisations to the Co-ordination Group for mutual recognition and decentralised procedures (CMDh) and be entirely financed by public funds.

Recommendation 14:

● **Develop proactive pharmacovigilance.** Spontaneous reporting enables the identification, after a time, of serious adverse effects that correspond to uncommon conditions (congenital malformations, agranulocytosis, anaphylactic shock, acute liver failure, etc.). In recent years however, a number of serious adverse reactions corresponding to common diseases have been identified, but only after a long delay (breast cancer with hormone replacement therapy, cardiovascular effects with cyclooxygenase-2 inhibitors (anti-inflammatory drugs), bone fracture with proton pump inhibitors (anti-ulcer medication), etc.). Because these adverse effects correspond to common diseases, they are seldom reported spontaneously, and were often discovered through observational studies or during clinical trials. Proactive pharmacovigilance is needed as a complement to the spontaneous reporting system: the drug regulatory agencies are responsible for analysing clinical trials (meta-analyses) in order to identify and quantify the risks associated with the use of medicines, and for proactively organising observational studies.

Data and transparency

Recommendation 15:

● **Increase the transparency of pharmacovigilance decisions.** A few of the European Commission's proposals will increase transparency and should be kept:

- by means of the European medicines safety web-portal: making risk management systems and the current list of drugs under intensive monitoring publicly accessible (*proposed article 106 of the Directive*), making recommendations, opinions and decisions of licensing Committees (CHMP and CMDh) publicly accessible (*proposed article 107m of the Directive*),

- publicly announcing the initiation of the "pharmacovigilance urgent measures" procedure and providing the possibility to participate in the PRAAC's hearings (*proposed article 107k (1) and (2) of the Directive*)

- making the PRAAC's recommendations publicly accessible (*proposed article 107r*).

In addition, public access must also be guaranteed as soon as possible for the following types of pharmacovigilance data:

- written requests from the authorities to pharmaceutical companies for post-authorisation safety studies, written explanations from the company about this requirement, the authorities' decision (confirmation or withdrawal of the requirement in question by the national competent authority) (*proposed article 22a of the Directive*) (r);

- the company's proposed post-authorisation study protocol, any letters of objection from the competent authority about the draft protocol or recommendations on the draft protocol, and any major amendments to the protocol (*proposed article 107o of the Directive*);

r- 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.

- final reports of post-authorisation safety studies (not just an abstract of the results of the post-authorisation study made public at the discretion of the competent authority) (*proposed article 107q of the Directive*);
- written requests from the authorities to pharmaceutical companies for risk management systems, written explanations from the company about this requirement, the authorities' decision (confirmation or withdrawal of the requirement in question by the national competent authority) (*proposed article 104a of the Directive*) (r);
- the full content of the Eudravigilance database, in a usable format (*proposed article 107a (2) of the Directive*) (see recommendation 8 above);
- the periodic safety update reports (PSURs) submitted to the regulatory authorities by pharmaceutical companies;
- assessment reports of the PSURs prepared by the national health authorities, including data on consumption, which is essential for evaluation of the level of exposure of the population;
- scientific assessment reports of the risk-benefit balance of medicines prepared by health authorities taking all the available data into account (*proposition d'article 107 e*);
- the agenda and detailed minutes (word-for-word transcription) of the meetings of the CHMP, the PRAAC (European pharmacovigilance committee) and the "coordination groups" (CMDh and "pharmacovigilance risk assessment coordination group") (not just an abstract of the PRAAC's meetings (*proposed article 26 of the Regulation*));
- the opinion of the CMDh when the PRAAC issues recommendations for the variation, suspension or revocation of a drug's marketing authorisation (*proposed article 107r*).

The International Society of Drug Bulletins

The Medicines in Europe Forum

Joint analysis; october 2009



International Society of Drug Bulletins (ISDB). International Society of Drug Bulletins (ISDB), founded in 1986, is a world wide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently, it has 79 members in 40 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org.



Medicines in Europe Forum (MIEF). Founded in March 2002, the Medicines in Europe Forum brings together 60 member organisations from 12 countries of the European Union. It is composed of four major groups active in the healthcare field: patients' groups, family and consumer groups, mutual health insurance providers and organisations of healthcare professionals. The movement is unprecedented in the history of the European Union (for more information, please see the website <http://english.prescrire.org/spip.php?article350>). Contact: europedumedicament@free.fr.

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