



EU Commission's proposals on pharmacovigilance dismantle the entire system

Executive summary

In December 2008, the European Commission published a proposed Regulation and Directive concerning pharmacovigilance.

In spite of recent public health disasters, several of the proposed measures will weaken rather than strengthen the European pharmacovigilance system:

- rather than stepping up the post-authorisation evaluation of all drugs by reinforcing independent national and regional pharmacovigilance systems, an **increased use of "risk management systems"** is proposed. Experience reveals that the latter often act as an excuse for dangerous cutbacks in the evaluations performed prior to licensing;
- **end of the requirement for public funding of pharmacovigilance activities**, relegating the Member States' pharmacovigilance systems to the level of service providers for pharmaceutical companies, while pharmaceutical companies have a vested interest in delaying the disclosure of pharmacovigilance data;
- **tightening of the pharmaceutical companies' stranglehold on the collection, analysis and interpretation of data**, bypassing the Member States' public pharmacovigilance systems, depriving society of their expertise and risking their demise in the medium term;
- **setting up a European Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) with no authority or autonomy, nor the adequate means to act effectively;**
- **providing for the dilution of pharmacovigilance data**, which will be stored directly in an electronic "mega-database" - Eudravigilance - depriving independent experts from local pharmacovigilance systems of information that is crucial to the in-depth analysis of adverse event reports;
- **maintaining the lack of transparency surrounding pharmacovigilance data** (for example, no access to periodic safety update reports (PSURs)), on the pretext of its "commercially confidentiality", whereas, in fact, these are scientific data on adverse effects suffered by patients/consumers and a matter of public interest.

To improve the safety of European citizens, the priorities must be:

- to protect patients from exposure to the adverse effects of drugs that provide no therapeutic advance, by **requiring**

that the therapeutic advance of a drug relative to existing treatments be demonstrated in order to obtain marketing authorisation;

- to **guarantee public funding** for the European pharmacovigilance Committee and the national and regional pharmacovigilance systems of Member States, in order to allow them, in full independency, to fulfil their responsibility in terms of population protection. The effectiveness of their work will lead to more timely decisions (i.e. strengthened monitoring or market withdrawal of medicines found to have an unfavourable risk-benefit balance), and consequently important savings (i.e. reduction of the numbers of hospital admissions, days of sick leave, and medical consultations caused by adverse reactions due to medicines);
- to **develop the intellectual independence of health authorities from pharmaceutical industry**, through stricter control of conflicts of interest and by limiting the influence of the biased International Conference on Harmonisation (ICH) standards;
- to **redefine the PRAAC as a European pharmacovigilance committee, which would be an instrument for cooperation between the pharmacovigilance systems of Member States**, with the authority to propose directly to the European Commission: changes to summaries of product characteristics (SPCs) and patient leaflets; or the market withdrawal of medicines with unfavourable risk-benefit balance;
- to **organise public, Europe-wide collection of high-quality adverse event reports** (i.e. via a database such as Eudravigilance), where data would be entered exclusively by the pharmacovigilance systems of Member States in order to benefit from their expertise. The data must be made available, in a usable format, to all European citizens;
- to **make health authorities accountable for the effective use of European pharmacovigilance data** (improving feedback to reporters, faster decision-making on measures to protect their citizens, etc.);
- to **increase the transparency** of pharmacovigilance activities.

As long as they are profoundly amended, the EU Commission proposals on pharmacovigilance can be refocused to defend the public interest.

Signatories



AIM. *The Association Internationale de la Mutualité (AIM)* is a grouping of autonomous health insurance and social protection bodies operating according to the principles of solidarity and non-profit-making orientation. Currently, AIM's membership consists of 41 national federations representing 29 countries. In Europe, they provide social coverage against sickness and other risks to more than 150 million people. AIM strives via its network to make an active contribution to the preservation and improvement of access to health care for everyone. More info: www.aim-mutual.org. Contact: rita.kessler@aim-mutual.org.



ESIP. *The European Social Insurance Platform (ESIP)* represents a strategic alliance of over 40 national statutory social security organisations in 16 EU Member States and Switzerland. ESIP's mission is to preserve high profile social security for Europe, to reinforce solidarity based social insurance systems, and to maintain European social protection quality. More info: www.esip.org. Contact: esip@esip.org.
Note: ESIP members support this position in so far as the subject matter lies within their field of competence.



HAI Europe. Health Action International (HAI) is an independent global network of health, consumer and development organisations working to increase access to essential medicines and improve rational use. More info: www.haiweb.org. Contact: teresa@haiweb.org.



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, ISDB has 79 members in 40 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org.



MiEF. Medicines in Europe Forum (MiEF), launched in March 2002, covers 12 European Member States. It includes more than 70 member organizations representing the four key players on the health field, i.e. patients groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is unique in the history of the EU, and it certainly reflects the important stakes and expectations regarding European medicines policy. Admittedly, medicines are no simple consumer goods, and the Union represents an opportunity for European citizens when it comes to guarantees of efficacy, safety and pricing. Contact: europedumedicament@free.fr.

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Full text

A series of public health disasters have served as a constant reminder that effective pharmacovigilance is crucial for the protection of citizens (a). They show that drug alerts and decisions are often delayed in order to protect, for as long as possible, the interests of the companies whose drugs are implicated (see below). The human and financial costs of the adverse effects of drugs are high, and are borne by society: adverse effects are responsible for at least 5% of hospital admissions and the 5th ranking cause of hospital deaths according to the European Commission itself.

On 10 December 2008, the European Commission published a proposed Regulation and Directive concerning pharmacovigilance (1,2).

Although these proposals are less disastrous than the ones submitted for consultation in February 2008 (b), they are grossly inadequate if pharmacovigilance is to be genuinely strengthened in Europe.

The current situation: pharmacovigilance needs to be strengthened

As of 2009, the way pharmacovigilance is organised in Europe does not ensure the protection of European citizens, mainly because the economic interests of pharmaceutical companies too often take priority over public health.

Unjustified exposure of patients to avoidable adverse effects. The vast majority of new drugs that are brought to the market provide no real advance (3). Some even constitute a step backwards, by exposing patients unnecessarily to adverse effects when other safer treatments already exist for the same indications (c). Moreover, drugs are licensed increasingly prematurely, at the expense of proper evaluation, leading to more pharmacovigilance issues further down the line (4).

Economic interests and withholding of data. Once a drug is licensed, its economic profitability depends on the con-

fidence healthcare professionals and patients have in the drug. When a pharmacovigilance problem emerges, the fall in the sales of the product and in the share price of the company involved reveals the extent to which such problems damage its economic interests. Pharmaceutical companies therefore have an obvious interest in withholding this kind of data, as well as unfavourable results from clinical trials for as long as they can in order to continue selling their products for as long as possible. This was the case during the recent scandals involving rofecoxib (Vioxx[®]), olanzapine (Zyprexa[®]) and quetiapine (Seroquel[®]), etc. While such a strategy resulted in a gain of time and increased sales for pharmaceutical companies, it has also resulted in thousands of deaths in the population exposed to these drugs (d).

Pharmacovigilance systems need strengthening. Many Member States have set up regional pharmacovigilance centres (France, Italy, Netherlands, Poland, Portugal, Spain, the United Kingdom). Countries with smaller populations often have a national pharmacovigilance centre, often within their drug regulatory agency (Belgium, Croatia, Estonia, Greece and Luxembourg, etc.). Germany has several centres, some specialising in a particular type of adverse effect (for example, the centre for the documentation of serious cutaneous reactions). Healthcare professionals (doctors and pharmacists in particular) are required to report any observed adverse events to these bodies, and particularly serious and/or unexpected adverse effects.

In spite of the under-reporting of adverse effects by healthcare professionals (5), national and regional centres manage to bring problems to light through the expertise of teams specialised in pharmacology, which are able to assess the causality of the adverse events reported due to their proximity to both the population and healthcare professionals. This proximity, in terms of language and knowledge of the lifestyle and habits of patients, enables easy contact with reporters, for example by telephone. Teams can thereby obtain valuable additional information, building up the scientific data contained in the original report and making it more informative (e). Without this step, incomplete reports cannot be properly ►►

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

b- These proposals provoked massive opposition. They provided for wider use of premature market authorisation for insufficiently evaluated drugs, and delegation to drug companies (even though they are both judges and judged) of activities that fall under the responsibility of public pharmacovigilance systems (ref. 8).

c- Since 1965 in Europe, the conditions for obtaining marketing authorisation are demonstration of the drug's efficacy, safety and quality. However the new drug is not required to be shown to be more effective or less dangerous than existing drugs already licensed for the same therapeutic indications.

d- For example, in 2000, data from the Vigor trial revealed an increased rate of infarction in patients taking the anti-inflammatory drug Vioxx[®] (rofecoxib). 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 these initial results and the withdrawal of Vioxx[®], 4 years, tens of thousands of cardiovascular events occurred, some of which were fatal.

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.

Other scandals include paroxetine (Paxil[®]/Seroxat[®]) from the company GlaxoSmithKline, citalopram (Celexa[®]) and escitalopram (Lexapro[®]) from the company Forest Labs, quetiapine (Seroquel[®]) from the company AstraZeneca, etc. And the list continues to grow.

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

► analysed, and the information they contain is lost.

The alerts generated by pharmacovigilance centres enable national authorities to adopt necessary measures in order to protect their population (for example, the withdrawal by several EU countries of the combination dextropropoxyphene + paracetamol in 2005, or nimesulide from 2002) (f). These market withdrawals are strong signals to other countries and the European Medicines Agency (EMA).

However, national authorities are increasingly reluctant to take up responsibilities to protect their population. They often hold back, waiting for the EMA's ruling before reacting, perhaps due to fear of going against the EMA, other Member States' authorities or pharmaceutical companies. Some countries are still waiting for the results of the endless arbitration procedure on the combination dextropropoxyphene + paracetamol. This process started in early 2008, in response to several hundred deaths due to overdoses with small intakes of the drug. Most notably, this particular combination does not provide a therapeutic advantage over other better-tolerated analgesics.

Drug regulatory agencies acting as service providers for pharmaceutical companies: delays and lack of transparency. At present, unacceptable delays are observed before market withdrawal, even after serious adverse effects have been witnessed, for instance in the cases of nimesulide (g), rimonabant (Acomplia[®]) (h), and rofecoxib (Vioxx[®]) (i).

One has to realise that the licensing committees of national drug agencies and of the EMA (CHMP) have 2 types of conflicts of interest with regard to pharmaceutical companies:

– a financial conflict of interest: pharmaceutical companies are the main clients of the drug regulatory agencies, the former funding the latter through the fees they pay (j). And many of the experts consulted by the drug regulatory agencies are also often working for drug companies (k);

– and an intellectual conflict of interest: the drug licensing committees are obviously reluctant to decide to withdraw a drug from the market that they themselves approved, because this withdrawal would call into question their evaluation work and would mean going back on their original decision.

In short. In light of the current context, we were expecting the European Commission proposals to:

– put an end to the exposure of the population to the adverse effects of drugs that provide no therapeutic advance, by setting up more stringent requirements for obtaining marketing authorisation (MA);

– reinforce the public expertise of nation-

al and regional pharmacovigilance centres and their independence from the licensing committees of the drug regulatory agencies;

– stimulate more active pharmacovigilance in Europe: with greater transparency; greater dissemination of reviews and alerts; more feedback to health professionals and patients reporting adverse events in order to encourage reporting; more active and sustained cooperation between pharmacovigilance centres.

Unfortunately, the European Commission's proposals published in December 2008 are grossly inadequate, and even threaten the existing system.

The European Commission's proposals: apparent "technical" measures, actual threats to the system

The proposals of the Regulation and Directive concerning pharmacovigilance, published by the European Commission in December 2008, are presented as being a series of "technical" measures (1,2). In reality, their scope is much wider as they concern every stage of the commercialisation of drugs in Europe: from evaluation to marketing authorisation, including monitoring and product information.

Our analysis of the key points of these proposals is presented below, along with → *our concrete proposals for improvements.*

"Risk management": will dangerously premature marketing authorisations become the norm? The evaluation of drugs prior to marketing authorisation (MA) only provides a general idea of their adverse effects, because the drugs have been tested for a limited time on a selected sample of patients. The role of pharmacovigilance is to obtain further knowledge of adverse effects so as to limit harm to real-life patients. Pharmacovigilance is an observational scientific discipline, which upholds the interests of patients as its priority.

The European Commission's proposals provide for the possibility of more widespread use of "risk management systems", particularly if there are concerns about risks "affecting the risk-benefit balance of an authorised medicinal product", and which should be "proportionate to the (...) risks" (proposed amendment to article 1(2) point (e) and proposed article 104(3) point (c) and 104a of the Directive, and proposed article 21 of the Regulation). According to the proposal, if concerns exist about the safety of a drug being authorised for "exceptional circumstances", it is also proposed that a marketing authorisation can be granted provided that post-authorisation studies are to be conducted (this condition has to be stated in the risk

management plan) (proposed article 22a of the Directive and article 10a of the Regulation). 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 request (proposed articles 22a and 104a of the Directive) (l).

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[®]) and varenicline (Chantix[®]/Champix[®]) illustrate this point (m). Based on their ►►

f- For example, from as early as 2005, the United Kingdom and Sweden decided to withdraw dextropropoxyphene combinations from the market following several hundreds of deaths through overdose, some of which were rather minor accidental overdoses. Finland and Spain withdrew nimesulide (Nexen[®]) from their markets in 2002, and were joined in 2007 by Ireland and Belgium.

g- In 2007, after several months of prevarication, the EMA's drug licensing committee (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.

h- Similarly, rimonabant was withdrawn from the European market only 2 years after its marketing authorisation in obesity due to an unfavourable risk-benefit balance (see note (m) for more details). The US drug regulatory agency (FDA), on the other hand, had refused to approve rimonabant.

i- This anti-inflammatory drug was only withdrawn from the European market, on the company's initiative, 4 years after the analysis of the results from a trial by the US drug regulatory agency (the FDA) had shown an increased number of serious cardiovascular events.

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

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

l- 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.

► 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.

Minimising the harm of adverse effects demands a more stringent pre-authorisation evaluation. Such a system should only grant marketing authorisation to medicines that offer added therapeutic value. The European Commission unfortunately says nothing about these necessary improvements to pre-authorisation evaluation.

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 evaluations (n).

The Commission is in fact proposing to make it easier for Member States to grant premature authorisations, accompanied by “conditions”: for example it will be enough to stipulate that post-authorisation safety studies are to be conducted (*proposed article 21a of the Directive*). In contrast to the current provisions for centralised marketing authorisation procedures, it will no longer be necessary to prove that there is an unmet public health need (patients with no further treatment options, for example) when requesting such “conditional” marketing authorisations (o).

Neither is it specified that these authorisations will only be maintained if the stipulated conditions are met. However, years of experience of simplifying and accelerating marketing authorisations procedures show that, in Europe, the US and Canada, pharmaceutical companies do not honour their commitments on post-authorisation evaluation (6,7). The proposal to include prematurely authorised drugs on a list of products “under intensive monitoring” is not sufficiently reassuring (*proposed article 23 of the Regulation*).

Proposed improvements:

→ *All drugs available on the European market should be carefully monitored by pharmacovigilance systems. The efficacy of these systems must be strengthened at both European and national levels (see below).*

→ *Unjustified conditional marketing authorisations must not become the norm, even when accompanied by risk management systems and post-authorisation studies. Such practice would expose patients to adverse effects which could be undetected or underestimated at the time of the marketing authorisation (proposed article 21a of the Directive). Risk management systems will only be able to reinforce pharmacovigilance if designed and conducted under health authorities’ close supervision. Risk management systems aims should be to identify any adverse effects, as well as their frequency and severity (also long-term), in*

order to enable reactive decision-making by health agencies. These decisions will prevent their harmful consequences and their recurrence.

→ *In the current context, where direct-to-patient communication by drug companies is being deregulated (proliferation of “disease management” or “patient education” 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 drug.*

A public interest role being sold to pharmaceutical companies. The adverse effects of drugs are effects suffered by patients, to the detriment of their health. Knowledge about the effects that medicines have on patients is a matter of public interest.

Public authorities are responsible for monitoring adverse effects: because they are accountable to protect public health, because they have assumed responsibility for granting marketing authorisations.

However, the Commission’s proposals go against the spirit of transparency of Directive 2004/27/EC and Regulation (EC) 726/2004 (p) ending the requirement for public funding, both at national and community level (*proposed article 105 of the Directive and proposed amendment to article 67 of the Regulation*).

Worse still, the European Commission foresees that the funding of pharmacovigilance activities through the fees paid by pharmaceutical companies should not be excluded. Yet, most notably pharmaceutical companies have an inherent vested interest in delaying the disclosure of pharmacovigilance data!

Entrusting the funding of pharmacovigilance to pharmaceutical companies is harmful to the population (q). It is also detrimental to health budgets, as the above mentioned practices would increase the costs of treating adverse drug reactions, either from medicines which have been left too long on the market, or have not been adequately monitored.

Proposed improvements:

→ *The requirement for public funding of pharmacovigilance, which is a public health activity, must be maintained (Article 67.4 of Regulation (EC) 726/2004) and applied by Member States, particularly considering the savings to be made: a decrease in adverse drug reactions means a reduction in hospitalisations, days of sick leave, and medical consultations.*

The pharmaceutical companies’ stronghold over data collection. The principle underlying the European Commission’s proposal to abandon pharmacovigilance to drug companies is to “give

responsibility” to pharmaceutical companies for monitoring the adverse effects of “their” drugs. But experience shows that entrusting pharmaceutical companies with the task of collecting and analysing the data, issuing alerts, and providing information on the adverse effects of their drugs, puts them in an unacceptable position due to their obvious conflicts of interest. Indeed, many recent examples serve as reminders that, in a context of impunity, the producer’s sense of responsibility is often overcome by the enticement to withhold data or delay its disclosure, so ►►

m- In the face of reports of adverse effects (increased suicide risk) and deaths after rimonabant (Acomplia[®]) 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[®]/Champix[®]), 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.).

n- 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).

o- With regards to centralised marketing authorisation procedures, Regulation (EC) 507/2006 specifies that a conditional marketing authorisation in principle may only be granted if “the risk-benefit balance of the medicinal product (...) is positive; (...) unmet medical needs will be fulfilled; the benefit to public health (...) outweighs the risk inherent in the fact that additional data are still required” (article 14.7). Furthermore, these conditional marketing authorisations must be re-assessed annually, and it is stated on the package leaflet that renewal of the marketing authorisation is dependent on the company fulfilling the conditions that were set.

p- The regulations introduced in 2004 increased the resources allotted to pharmacovigilance by requiring its public funding: “activities relating to pharmacovigilance (...) shall receive adequate public funding commensurate with the tasks conferred” (article 67.4 of Regulation (EC) 726/2004). In practice, this requirement for public funding needs is not yet fully applied in many Member States.

q- The declared aim of marketing consultants in the field of risk management is to “make pharmacovigilance the most creative marketing department” (ref. 9,10).

► as to avoid decisions that would adversely affect sales (d, r).

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.

However, the European Commission's proposals unearth dangerous opportunities for drug companies to bypass the public pharmacovigilance systems of each country, then to gradually replace them, at the risk of leading to their demise in the medium term. The EU Commission proposed in fact that healthcare professionals may be authorised to send their reports only to drug companies: "The Member States shall take all appropriate measures to encourage doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority or the marketing authorisation holder" (proposed article 102(1) of Directive). This measure enables the Commission to state in its impact assessment that the pharmacovigilance proposals will not involve great additional cost to Member States or the EMEA. It opens indeed the possibility that pharmacovigilance systems' current missions (recording and analysing of the health professional reports) will be subcontracted and progressively abandoned to pharmaceutical companies. This will lead to a reduction of the human resources employed by the public pharmacovigilance systems, or to their reallocation to other tasks.

The Commission also proposes that pharmaceutical companies receive healthcare professionals' and patients' reports (proposed article 107(1) and (2)). Companies will be responsible for sending these reports to "a single point within the Community" (Eudravigilance database) (proposed article 107(1)). This arrangement provides an opportunity for drug companies to manipulate the data. Above all, a sole, supra-national collection of reports dilutes the data and deprives 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. While it is proposed that some pharmacovigilance centres could consult the Eudravigilance database, they will only access the registered data, disconnected from proximity information or from information about the context, which will lead to a considerable loss of information.

Proposed improvements:

→ *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.*

Tightening drug companies' stronghold on data interpretation.

When it comes to interpreting the data, it is proposed that Member States may hand over the "follow up of such reports" to drug companies (proposed article 107(4)). In this case, pharmaceutical companies would be both defendant and jury charged with assessing the change, if any, in their product's risk-benefit balance (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)).

The European Commission's proposals grants the authorities the role of "checking" the PSURs through an assessment, but these PSURs are still compiled by drug companies (proposed article 107d and e) (s). Above all, the European Commission's proposals blur the roles of drug manufacturers, regulators and experts.

The subcontracting of data interpretation to drug companies is a major default in the current pharmacovigilance system. Enlarging these subcontracting arrangements would further endanger patients by stripping the health authority of the remainder of their authority, expertise, credibility and autonomy.

The Commission's proposals require the submission of one PSUR for the entire Community, at a frequency that is "appropriate" to the drug's risk profile. Pharmaceutical companies will have the opportunity to contest this frequency (proposed article 107c(6) point (c)).

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)). However, dramatic examples of discovered adverse effects (carcinogenicity, genotoxicity) are not rare, even 30 years after obtaining marketing authorisation (t). 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.

Moreover, the Commission's proposals increase the conceptual and technical dependence of health authorities on drug companies, through compliance with International Conference on Harmonisation (ICH) standards, which is an entity mainly composed by drug company representatives and heads of drug regulatory agencies (proposed article 101(4), proposed article 108).

Proposed improvements:

→ *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, 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.*

→ *Even for so called "well-established" medicines, periodic safety update reports (PSURs) must be submitted regularly, at least every 5 years;*

→ *The organisation of the European pharmacovigilance system will be based on European Good Pharmacovigilance Practices (GVP). GVP must be formulated primarily with the needs of European citizens in mind and from a scientific perspective. It must not be biased from inception by demanding compliance with existing ►►*

r- For example, in March 2008, after 4 and a half years of inquiries, the British Medicines and Healthcare products Regulatory Agency (MHRA) finally gave up pursuing the company GlaxoSmithKline for withholding pharmacovigilance data concerning paroxetine (Seroxat[®]) in children, due to an inadequate regulatory framework ("legal vacuum" surrounding the drug companies' responsibility to provide information to the authorities about off-label use of their drugs).

s- Pharmaceutical companies furthermore are entitled to have access to the assessment report produced by the authorities, which must be sent to them at the same time as it is submitted to the European pharmacovigilance risk assessment advisory committee (PRAAC). It is also stipulated that the Committee must take into account the comments presented by pharmaceutical companies (proposed article 107e(2) and (3)).

t- 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 wall 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.

► **ICH standards (proposed article 108).** On the contrary, GVP should serve as a basis on which the ICH standards are redefined, with the protection of the population held as a higher priority.

Setting up a European Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) with neither authority nor autonomy. Since 2004, the EMEA has particular responsibility, through its Committees, for the “*coordination of the supervision of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products (...); ensuring the collation and dissemination of information on adverse reactions to medicinal products authorised in the Community by means of a database permanently accessible to all Member States; health professionals, marketing authorisation holders and the public have appropriate levels of access to this database (...); assisting Member States with the rapid communication of information*” (article 57 points (c) to (e) of Regulation (EC) 726/2004). In order to achieve this, the EMEA had set up a Pharmacovigilance Working Party (PhWP) to help the medicines licensing committee (CHMP).

The current EU Commission’s proposal foresees that a European Pharmacovigilance Risk Assessment Advisory Committee (PRAAC) will replace this working party (proposed amendment to article 27 of the Directive and to article 56(1)(aa) of the Regulation).

However in practice, the role of the PRAAC will still be limited to:

– studying the assessment reports prepared by Member States (in the case of decentralised or mutual recognition marketing authorisation procedures) or rapporteurs (in the case of centralised marketing authorisation procedures). These reports are based on the periodic safety update reports (PSURs) provided by drug companies (proposed article 107e(2) of the Directive);

– evaluating community pharmacovigilance procedures in order to issue “recommendations” (for example, when a Member State wants to suspend or withdraw a medicine from the market for safety-related reasons) (proposed article 107k(2) and (3) of the Directive);

– evaluating the post-authorisation safety studies protocols for research which is to be conducted in more than one Member State (proposed article 107o of the Directive) as well as assessing their findings (only on the base of a summary of the results provided by the pharmaceutical company), to issue “recommendations” (proposed article 107q).

The only real advance is that, as part of the EU pharmacovigilance procedures, the PRAAC would be able to organise public hearings, which would contribute to greater

transparency (proposed article 107k(2) of the Directive).

However, the decision to propose to the European Commission to maintain, modify or suspend a marketing authorisation would be up either to the “Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human” (CMDh), composed of one representative from each Member State, or, for centralised authorisation procedures, the “Committee for Medicinal Products for Human Use” (CHMP). This despite their intellectual conflicts of interest (u). The CHMP and CMDh are not required to implement the PRAAC’s recommendations – this committee will then have no authority.

When “alerted” by health agencies or pharmaceutical companies (by means of procedures and responsibilities that have not been clarified), the PRAAC is expected to prioritise “*indications of new or changing risks or changes to the risk-benefit balance*” by exploring the Eudravigilance database, in order to find additional data (proposed article 107h).

It is difficult to imagine how a committee reliant on fees paid by pharmaceutical companies (proposed amendment of article 67 of the Regulation) and with limited human resources (15 members, not even one per Member State) and no authority, will be able to use effectively the Eudravigilance database. Particularly as the Eudravigilance database runs a strong risk of being a “hotch-potch” of unusable raw data, possibly in a variety of languages (or, if only filled in English by too many different non specialised sources, with the risk of a loss of information due to translation default because this field is technical and requires precisions for the analysis), and lacking a fine-tuning from local pharmacovigilance systems.

We welcome provisions on how the procedure through which urgent pharmacovigilance measures will be applied, and particularly the details on the timetable (proposed articles 107 to 107l of the Directive). But rather than increasing the powers of the CMDh and the CHMP, it is those of the new PRAAC that need to be enhanced if it is to be a truly effective body.

Proposed improvements:

→ **The PRAAC must be defined as a European instrument for cooperation between national pharmacovigilance systems, intellectually and hierarchically independent from drug licensing committees. It should be renamed as the “European pharmacovigilance committee”.**

→ **This European pharmacovigilance committee 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, 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.**

Developing independent expertise.

Many countries already have public pharmacovigilance systems that have proved their effectiveness by uncovering adverse effects, even in the long-term. These pharmacovigilance centres, some of which are linked to the teaching hospitals system of their country, establish long-term pharmacovigilance research policies. They are also able to conduct in-depth analysis of suspected adverse effects and obtain findings about the first indications of their causality. In addition, they set up surveys to further assess the magnitude of the events and their causality. Yet, the Commission’s proposal completely ignores the essential work developed by these centres (v).

On the contrary, the European Commission intends to construct an organisation that will deprive these specialised teams from the data, by allowing health-care practitioners and patients to report adverse effects directly and solely to drug companies (proposed article 102(1) of the Directive) (see above). In the proposal, States may even choose to delegate their pharmacovigilance activities to another Member State (proposed article 103 of the Directive). This will further weaken their expertise and exacerbate the problem of under-reporting within specific countries, rather than encouraging them to build up ►►

u- These bodies, which would have licensed the implicated drug in the first place, would find it difficult to raise doubts about their original decision and overturn it.

v- In the Commission’s proposal, which focuses on the role of drug companies in the follow-up of their recent drugs, it is hard to imagine for example how the risk-benefit balance of non-steroidal anti-inflammatory drugs during pregnancy, or the belatedly identified consequences of in-utero exposure to diethylstilbestrol in women whose mothers received this drug while pregnant, could have been re-evaluated. It is also highly unlikely that companies will monitor products that are off-patent.

► their expertise through exchange with experienced teams from other Member States (w).

The proposed reform of European pharmacovigilance relies on a “fully electronic” approach (Eudravigilance database, web portals for reporting and public information), thus expecting financial savings for drug companies and the authorities.

This overlooks the fact that national pharmacovigilance system enable insightful analysis based on their expert knowledge of local population, their proximity to healthcare professionals and patients allows easy contact to collect additional valuable information to the reports. Centralising all reports at European level without regional or national analysis will result in the dilution of the data, hindering detailed analysis and interpretation, and finally making Eudravigilance database useless.

Proposed improvements:

→ *The central role of national or regional pharmacovigilance centres in the collection and analysis of spontaneous reports must be promoted and financed with public funds.*

→ *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.*

→ *The Commission’s proposal must be redirected to further strengthen:*

– *the existing pharmacovigilance systems, which must be given the resources, through adequate public funding, to conduct independent and quality expertise, and to fully engage in active pharmacovigilance, ;*

– *the coordination among current systems, by establishing a European pharmacovigilance committee (see above).*

Lack of transparency under the pretext of withholding “commercially confidential” information. Data on adverse effects experienced by patients are public scientific data. They need to be analysed and interpreted to prevent recurrence and lead to independent decision-making. Pharmacovigilance data are not commercial data to be collected by pharmaceutical companies as part of their marketing services.

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 Eudravigilance database for the public are not sufficient to ensure public access to pharmacovigilance data (x). For example, there

is no proposal to make PSURs public (these are a key resource in risk-benefit assessments). However, Regulation (EC) 1049/2001, on public access to documents from European institutions, clearly stipulates that these documents should already be publicly accessible. Drug regulatory agencies even refuse to make public their assessment reports of these PSURs in order to protect pharmaceutical companies’ commercial interests (y)! Within this scenario, how is it possible to understand and accept the rationale behind the authorities’ decision-making?

Furthermore, it is proposed that only the summaries of Committee meetings will be made available to the public (z), and not those of the Agencies’ working parties or the CMDh (*proposed article 26 of the Regulation*). Yet, article 126b of Directive 2004/27/EC on 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*”.

Proposed improvements:

→ *Adverse effects of medicines require proper action: collection and analysis by public national and international systems, in order to address the problem, as is the case for example of infectious diseases, which are monitored notably as part of the Euro-surveillance system.*

→ *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.*

→ *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; is considered that a “final decision” was not obtained cannot be removed from the minutes.*

Summary of our concrete proposals for an effective pharmacovigilance system

More stringent requirements for safer marketing authorisations. The conditions required for granting marketing authorisation must be improved. A new application for marketing authorisation should demonstrate that the new drug offers added therapeutic value, to avoid unnecessary exposure of the population to otherwise preventable harm. Such a requirement would redirect research and development to areas of unmet medical needs. It would represent an effective tool to end the current waste of resources, whereby large sums from the national health budgets are spent to finance, at high prices, medicines that offer no added therapeutic value or are even therapeutic regressions.

Provide authorities with the means to act independently from the industry. The (financial and intellectual) independence of health authorities from pharmaceutical companies is crucial. A key provision of the 2004 legislation establishes that pharmacovigilance activities are to “*receive adequate public funding commensurate with the tasks conferred*”. It is essential that this clause is maintained and finally implemented (67.4 of Regulation (EC) 726/2004). Stimulating the intellectual independence of authorities from pharmaceutical companies requires strict control of conflicts of interest and a re-assessment of position of the Internatio- ►►

w- How will these patients and healthcare professionals go about reporting adverse effects? Will they have to do it through the web portal of the system of the Member State to which their own State subcontracts its pharmacovigilance activities, in a language they do not understand? Will they have to do it via the drug companies present in their own country, but then what about drugs marketed by companies that are not present in their country?

x- Such access was already provided in 2004 (article 57 of Regulation (EC) 726/2004). In practice, as of 2009, citizens still do not have access to this database, and the proposed “appropriate access” for the public to Eudravigilance, as defined by the EMEA, is restrictive and grossly inadequate (ref. 11).

y- It is unacceptable to claim that data on drug consumption is “commercially confidential” information: such data are sold to drug companies by companies specialised in selling economic data. But in reality they are scientific data that can be used to evaluate the exposure of the population to adverse effects.

z- Committee for Medicinal Products for Human Use (CHMP), Committee on Orphan Medicinal Products, Committee on Herbal Medicinal Products, Paediatric Committee (Article 56 of Regulation (EC) 726/2004).

aa- Equivalent to the European Public Assessment Reports (EPARs) released by the European drug licensing committee (CHMP).

► nal Conference on Harmonisation (ICH) when drafting recommendations on medicines and pharmacovigilance.

Provide adequate resources to foster an effective public pharmacovigilance system. Effective pharmacovigilance requires genuine political will to set the following priorities:

- to redefine (and rename) the European pharmacovigilance committee as a European platform for cooperation between national pharmacovigilance systems;
- to grant the European pharmacovigilance committee the authority to feed proposals directly to the European Commission (namely withdrawals of drugs that have an unfavourable risk-benefit balance or changes to product information) ;
- to organise high-quality, Europe-wide, public collection of adverse event reports. This data collection could be set up as an electronic database, like Eudravigilance, and is to receive input solely from the Member States' pharmacovigilance systems, so as to benefit from their expertise;
- to make health authorities aware of their responsibilities regarding the effective use of European pharmacovigilance data, and in particular: to encourage healthcare professionals and patients to report adverse events, including improving feedback to reporters; to carry out proactive pharmacovigilance research; to speed up decision-making on measures aimed at protecting citizens;
- to make the data from the Eudravigilance database accessible to all European citizens, in their own language, provided patient anonymity is upheld;
- to monitor and control post-authorisation

studies, including those pertaining to "risk management systems". These studies must be conducted by independent teams and should no longer be used as an excuse for granting premature marketing authorisations;

- to have the power to impose real penalties on pharmaceutical companies that do not fulfil their pharmacovigilance obligations.

Increase transparency. The transparency regulations introduced in 2004 should be fully implemented. There are several measures that are simple to implement:

- to help identify adverse effects and recent pharmacovigilance decisions, by highlighting the key points and including them on the patient information leaflet in a different font type (in bold for example);
- to help identify drugs which have been authorised despite insufficient evidence, 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>*" (proposed amendment of article 11 of the Directive), and also by including 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;
- grant total public access to pharmacovigilance information: PSURs including data on consumption; complete PSUR assessment reports; Eudravigilance reports as well as periodic summaries prepared by the EMEA; requests for post-authorisation studies or risk management programmes, together with the pharmaceutical companies' responses;

- make public the agendas and full transcripts of meetings of the European pharmacovigilance committee and the detailed rationale behind pharmacovigilance decisions, including minority opinions and the detail of votes.

Conclusion

With the present proposals on pharmacovigilance, the European Commission aims to boost the competitiveness of pharmaceutical companies by granting easier and earlier marketing authorisations. Consequently, these attempts will dismantle the system and delay the detection of adverse effects as well as decisions that are required to protect public health - at least until drug companies have earned the anticipated "return on their investment".

In reality, the European Commission is abandoning its remit to protect European citizens (article 125 of the Treaty establishing the European Union) in order to protect the short-term economic interests of pharmaceutical companies; and holds back the development of a pharmaceutical industry that is truly innovative through a high level of quality.

We hope that our concrete proposals will help Members of the European Parliament, Health Ministers, and the European Commission's Directorate-General for Health and Consumers to improve the European Commission's proposals.

Provided that these legislative proposals are profoundly amended, they can be refocused to defend the public interest.



**Association
Internationale
de la Mutualité (AIM)**



**Health Action
International (HAI)
Europe**



**European Social
Insurance Platform
(ESIP)**



**Medicines in Europe
Forum (MIEF)**



**International Society
of Drug Bulletins
(ISDB)**

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