New European pharmacovigilance legislation: getting it right

Response to the European Commission's public consultation on legislative proposals for pharmacovigilance (deadline 1st February 2008) (1).

Executive summary

A series of public health disasters (from thalidomide in the 1960s to rofecoxib (Vioxx°) at the beginning of this century) have served to remind us that effective pharmacovigilance is crucial for the protection of citizens. Regrettably, the European Commission's proposed legislative changes, published on 5 December 2007, pose a serious threat to public health (1).

On the pretext of simplifying administrative procedures and "rationalising the system", the Commission's proposals undermine the European pharmacovigilance system and represent a major backward step for the evaluation of medicinal products.

Pre-authorisation evaluations of medicines: helping to boost the pharmaceutical firms' competitiveness while jeopardising patient safety

The European Commission's proposals will expose European citizens to medicines that have been less thoroughly evaluated prior to authorisation.

Cutting corners on marketing authorisations. The Commission's stated aim is to bring new medicines to market faster: *"Earlier product authorisation provides faster return on investment and, by reducing the cost of capital, the total cost of product development is reduced"*.

To achieve this, the Commission proposes to undermine the pre-authorisation evaluation by making conditional authorisations the norm rather than awarding them only in exceptional circumstances, when there is an urgent therapeutic need, as is currently the case (article 22 in the proposed amended Directive).

To foster this shift and at the same time reassure the public, the Commission is hiding behind the concept of "risk management systems", set up and piloted by pharmaceutical companies. Unfortunately, these "risk management systems" are not designed with patient safety as the key priority.

Having medicines approved even when *"therapeutic efficacy is insufficiently substantiated"*. The Commission is proposing to delete *"therapeutic efficacy is insufficiently substantiated"* from the list of reasons for refusing a marketing authorisation (article 26) or withdrawing a drug (articles 116 and 117).

However, only proven efficacy can in fact justify exposing patients to adverse effects.

Furthermore, how can the authorities evaluate the risk-benefit balance of a new drug if they do not have robust evidence of its efficacy?

Companies in charge of pharmacovigilance data: at every stage, at the cost of patient safety

Entrusting the pharmaceutical companies with the task of gathering and analysing data, issuing warnings and informing of their products' adverse effects is unacceptable due to in-built conflict of interests. And yet the Commission's proposals provide for the industry's intervention at every level of decision-making, putting them in the position of both judge and defendant.

Gathering risk evaluation data: minimal demands. The Commission is proposing that post-authorisation studies and risk management plans can only be requested by marketing authorisation committees under limited conditions, and that the "risk management" system shall *"be proportionate to the identified and potential risks taking into consideration the information available on the medicinal product"* (Article 8). Unexpected or delayed adverse effects, even when severe, are likely to be excluded from these systems, which are not designed to identify rare long-term adverse effects.

Routine data gathering: centralisation and dilution of responsibilities. The placing of pharmacovigilance responsibilities on the holder of the marketing authorisation, the parent company, threatens to remove the responsibility from those exploiting it at national level. The stipulations for data recording and processing are unclear and do not allow for any external monitoring. ▶▶

▶ Asking patients to notify directly to the companies adverse effects for intensively monitored drugs is unacceptable (article 59).

The companies' pharmacovigilance systems cannot under any circumstances become a substitute for national public pharmacovigilance systems which unequivocally serve public interest.

Subcontracting data monitoring to pharmaceutical companies: danger. The Commission plans to subcontract the monitoring of "*all available relevant data including data on Eudravigilance for signals of new or changing risks (…)*"to the firms (article 101l), even though they are both judge and defendant. It will also be up to the companies to alert the authorities in the event of new data likely to affect their product's risk-benefit balance (Article 101h).

Data analysis: lack of transparency. According to the Commission's proposal concerning the results of post-authorisation studies, it is up to the firms to: "*consider whether the results of the study impact on the product labelling*" (article 101h.1.i) or "*might influence the risk-benefit balance of the medicinal product*" (Article 101h.1.g). Subcontracting the interpretation of the data will result in the drug regulatory agencies losing their authority and expertise.

The decision-making process: the payer calls the tune... The 2004 Regulation strengthened the resources to be devoted to pharmacovigilance, insisting that it should be publicly funded to guarantee its independence, specifying that: "*Activities relating to pharmacovigilance, (…) shall receive adequate public funding commensurate with the tasks conferred*" (Article 67.4 of Regulation 726/2004 (EC).

The Commission is planning to abolish this requirement for adequate public funding and to allow pharmacovigilance to be directly funded by the firms through the marketing authorisation fees paid to the agencies (Article 101 c).

Information on adverse effects: blurring of roles. It is the authorities' responsibility to process and interpret data, and to communicate the results. At present, pharmaceutical companies are sending out "Dear Doctor" letters, thus speaking on behalf of health agencies, which is likely to result in abuses with companies trying to promote their medicines to health professionals.

Redressing the balance

The Medicines in Europe Forum, the *ISDB* and *HAI Europe* strongly condemn the Commission's proposals and call on it to re-focus its efforts and defend the public interest, in accordance with its remit to protect European citizens (Article 125 of the Treaty establishing the European Community).

The above organisations' concrete proposals to strengthen pharmacovigilance effectively fall into four categories:
– more stringent marketing authorisation criteria to ensure the approval of medicines offering a genuine therapeutic benefit;
– guaranteeing the transparency of pharmacovigilance data, information and decisions;
– granting authorities the means to be financially and morally independent from the pharmaceutical companies;
– ensuring resources are in place for effective pharmacovigilance systems.

These proposals are set out in detail on page 7.

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Full text

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Adverse effects caused by medicinal products diminish patients' quality of life, add to the number of hospitalisations, prolong hospital stays and increase mortality. Furthermore they represent a considerable financial burden for health systems (2).

Pharmacovigilance can be defined simply as "*the process for evaluating and improving the safety of medicines*" to prevent their adverse effects (2). The need for continuous monitoring of adverse effects emerged in the early 1960s, particularly after the *thalidomide* affair, which caused several thousand cases of atrophy of one or several limbs in babies born to women who had taken this drug during pregnancy (3). A number of subsequent public health disasters have served to remind us that effective pharmacovigilance is crucial for the protection of citizens: the *diethylstilbestrol* (DES) affair in the 1970s (cancer of the vagina and anomalies of the uterus in women exposed to this drug in the womb), that of *triazolam* in the 1980s (anterograde amnesia); and more recently, in the 2000s, those of *cerivastatin* (severe muscular disorders), *rofecoxib* (fatal cardiac events), so called 'selective' serotonin reuptake inhibitors (SSRIs) (increased risk of suicide), *olanzapine* (diabetes and metabolic disorders), *rosiglitazone* (fatal cardiac disorders) (4 to10).

In recent years, several major pharmacovigilance problems have thrown into question not only the effectiveness of pharmacovigilance systems, but also the authorities' commitment to protecting citizens by putting in place the necessary measures, such as quickly withdrawing drugs exposing patients to risks that are too high in relation to the expected benefits.

Changes to EU legislation to strengthen the pharmacovigilance system have been eagerly awaited.

It was hoped that the Commission's proposals published on 5 December 2007 would fulfil expectations. But these proposals are in fact hugely detrimental, further weakening the existing system and are another step in the direction of a general deregulation, under the pretence of "rationalisation" (11,12).

Consultation on pharmacovigilance in Europe: biased proposals

In March 2006, the European Commission launched a public consultation on the strengths and weakness of the EU system of pharmacovigilance, to which *Prescrire and Health Action International* (HAI) *Europe* contributed (13,14,15). The executive summary of the 48 contributions to this consultation was published in February 2007 (16), as was the Commission's 2-part strategy to "*improve and strengthen the monitoring of the safety of medicines*": improve the implementation of the current framework, then make proposals for changing the legal framework (17).

However, before providing the real means to apply the 2004 legislation more effectively (18), in December 2007, the European Commission proposed changes to the Regulation, some of which cancel out several major advances made in 2004, notably the need for pharmacovigilance activities to be publicly funded.

In the consultation published on 5 December 2007, several proposed major changes to the Regulation primarily favour the pharmaceutical companies' short-term interests, to the detriment of the public good (1). Many of these changes even contradict the recommendations formulated by the independent study on which the Commission claims to have based its proposals (19). The responses to the March 2006 consultation are only partially taken into consideration: for example, the establishment of a formal European pharmacovigilance committee is merely a sham since its authority will not actually be strengthened (16).

More worrying still, the Commission is seeking approval for the future amendments to articles 101a to 101p, designed to replace all the articles relating to pharmacovigilance of Title IX of the consolidated Directive 2001/83/EC, without a democratic endorsement through the codecision procedure, in accordance with the application of the principle of comitology (**a**) (Article 101q of the proposed Directive).

Pre-authorisation evaluation: sacrificed at the cost of patient protection

Since the 1965 Directive on Medicinal products, drug evaluation, the cornerstone of the EU legislative framework, has been characterised by the need to demonstrate a drug's quality, efficacy and safety prior to its obtaining a marketing authorisation. Recent years have seen a growing number of "waiving" procedures leading to product authorisations being granted faster and more easily: conditional marketing authorisations, product authorisations for exceptional circumstances, etc. (12).

The European Commission's pharmacovigilance proposal envisages making these procedures more widespread and goes even further down the route towards deregulation.

A growing trend towards cut-price marketing authorisations. Years of experience of faster, less stringent marketing authorisation procedures have shown that in both Europe and the USA, the pharmaceutical companies do not keep their promises when it comes to post-authorisation studies (**b**)(20,21). The Commission is aware of this, but its priority is protecting the companies' financial health rather than protecting public health. So "risk management plans" are proposed with the stated aim of bringing innovations to market faster, first and foremost to serve the firms' commercial interests: "*earlier product authorisation provides faster return on investment and, by reducing the cost of capital, the total cost of product development is reduced*" (Section 3.2.1 of the Introduction). ►►

a- As part of its remit to implement legislation, the Commission can adapt and modify so-called 'technical' measures without the approval of the European Parliament or of the Council to avoid "administrative burdens".

b- Once the marketing authorisation has been granted, the balance of power is in favour of the firms: the authorities, perhaps because they fear that the public – especially the patients using these treatments – will not understand their decisions, do not withdraw drugs from the market of the firms which have not fulfilled the requisite conditions, even though the continuation of this marketing authorisation was conditional on their doing so (refs 20,21).

"Risk management system": for whose benefit?

The consultation published on 5 December 2007 is presented as pertaining to the pharmacovigilance system, but it has a much broader scope, concerning every stage of the commercialisation of medicinal products in Europe: from evaluation to market launch, including monitoring and product information.

Under the guise of "modernisation", the Commission is promoting the concept of a "risk management system", which actually justifies the firms' intervention at each of these stages (1,2,3). The declared aim of this system is for "products to be authorised earlier in their development" (Section 3.2.1) (**a**).

The Commission thus creates confusion between the concepts of "risk management" and pharmacovigilance on the one hand, and "risk management" and the evaluation of medicinal products on the other.

Risk management is a forward-looking industrial and managerial discipline, focused on an activity or a product, which consists of assessing and pre-empting all the risks involved to enable the targets to be achieved (4). Here the targets are those of the pharmaceutical company managers and shareholders: allow early commercialisation of the medicinal product and encourage its widespread use while it is protected by a patent.

Pharmacovigilance however is a scientific discipline based on observation and focusing on the interaction between the drug and the patient; its purpose is to identify and rapidly warn of any adverse effects that pose a risk to patients, with the aim of preventing these effects from being replicated (5).

Drawing on methods associated with "risk management" too late in the day, when the issue is no longer one of managing presumed risks but of dealing with medicinal products' adverse effects, trivialises the analysis of adverse effects and reduces pharmacovigilance to an administrative process.

The conception of risk management presented by the Commission allows the pharmaceutical companies to adopt a product-oriented "risk management" approach designed primarily to protect the product (their medicines), but not to protect patients from drugs' adverse effects.

a- The declared objective of marketing consultants in the risk management field is to "make pharmacovigilance the most creative area of marketing" (refs 1,2).

References

1- "La gouvernance des risques : d´abord une volonté stratégique" *Pharmaceutiques,* March 2007: 79.

2- Price Waterhouse Coopers "Unlocking the power of pharmacovigilance: an adaptative approach to an evolving drug safety environment - Executive summary" April 2007. www.pwc.com/pharma 4 pages.

3- EMEA-CHMP "Guideline on risk management systems for medicinal products for human use" 14 November 2005: 32 pages.

4- Desroches A and coll. "Dictionnaire d'analyse et de gestion des risques" Lavoisier, Paris 2006; 480 pages.

5- International Society of Drug Bulletins "Berlin Declaration on Pharmacovigilance" The full text is available at www.isdbweb.org: 16 pages, 75 references.

► Specifically, the Commission is proposing to amend article 22 of Directive 2001/83/EC to make conditional marketing authorisations the rule rather than the exception: the notion of "*exceptional circumstances*" disappears, as do the restrictions specifying that this procedure is authorised solely for "*objective and verifiable reasons*" and that "*continuation of the authorisation shall be linked to the annual reassessment of these conditions*".

The development of risk management plans thus serves to reassure European citizens and to permit this slide towards conditional marketing authorisations becoming the norm, without even having to prove that there is a need (such as, for example, seriously ill patients for whom there is no effective treatment available) (22).

Proposal to remove the criterion of proven therapeutic efficacy: a major backward step. The criterion that a product must be of proven therapeutic efficacy in order to obtain authorisation was introduced after the thalidomide affair in the USA (Kefauver-Harris amendments in 1962), and in Europe in 1965. Only proven therapeutic efficacy can justify exposing the entire population to the risks of adverse effects when a new drug is authorised. It is essential to have an evaluation providing convincing evidence of the drug's efficacy in order to weigh up the risks of adverse effects (known, suspected and expected), in order to answer the question: what adverse effects are we prepared to accept given the drug's proven efficacy? And yet the Commission proposes to delete "*therapeutic efficacy is insufficiently substantiated*" from the list of reasons for withdrawing a drug (Articles 116 and 117) or refusing to grant a marketing authorisation (Article 26).

c- The recent cases of rofecoxib (Vioxx°) and olanzapine (Zyprexa°) are a reminder of the extent to which pharmacovigilance data can be damaging to the pharmaceutical companies, which will attempt to conceal the data for as long as possible. In 2000, for example, the data from the VIGOR trial revealed an excessive number of heart attacks in patients taking rofecoxib, an anti-inflammatory drug. The firm then put forward the hypothesis that the comparator drug used in this trial had a favourable cardiovascular effect. The time lost between these initial results and the withdrawal of rofecoxib, four years later, resulted in tens of thousands of sometimes fatal cardiovascular events (ref 7). Another more recent example: in 2007, Lilly paid out several tens of thousands of dollars compensation each to 28,000 plaintiffs in the United States, who accused the firm of not having informed them of the adverse effects of olanzapine, a neuroleptic which turned out to cause diabetes and severe metabolic disorders, even though Lilly was aware of this problem (ref 9).

Pharmaceutical companies' control on pharmacovigilance data: at every stage

Once their medicinal product is on the market, the companies' profitability depends on caregivers' and patients' trust in it. When a pharmacovigilance case emerges, the value of the manufacturer's shares on the stock market plummets, revealing the extent to which these cases can damage the pharmaceutical firms' commercial interests (**c**)(7,9).

Entrusting the pharmaceutical companies with the task of gathering and analysing data, issuing warnings and informing about their medicinal products' adverse effects is to put them in an untenable situation with a major conflict of interests. And yet, the Commission proposes to do just that.

Gathering risk evaluation data: minimal criteria. The Commission's proposals are that post-authorisation studies and risk management plans respectively can only be requested under limited conditions: if there are serious concerns about the risks affecting authorised product's risk-benefit balance, after having heard the firm's explanations (Article 101g and Article 101p) (**d**,**e**).

This prerogative falls to the authority responsible for granting the marketing authorisation (Committee for Medicinal Products for Human Use (CHMP) at European level, or the national marketing authorisation committees), and not the

d- The notion of "safety concern" has been defined in a restricted way by the European Federation of Pharmaceutical Industries Associations (EFPIA) in its response to the previous consultation: "any new safety information which might [probably] influence the evaluation of the benefits and risks of the product as opposed to a 'signal' (any new safety information [for which the impact on the risk-benefit of the product hasn't been analysed yet]). Only safety concerns should qualify for regulatory reporting from the MAH to the authorities, and vice versa as appropriate" (ref. 31).

e- Summer 2007, the controversy over the US legislation on the renewal of the fees paid by the firms to the Food and Drug Administration (FDA) to have their marketing authorisation applications accelerated (Prescription Drug User Free Act, PDUFA) and of the legislation on drug safety revealed the pharmaceutical companies' opposition to the funding of post-market monitoring (ref 32,33).

European or the national pharmacovigilance Committees, which would be more appropriate.

The draft specifies that this system shall "*be proportionate to the identified and potential risks taking into consideration the information available on the medicinal product*" (Article 8). Unexpected adverse effects are likely to be excluded from the scope of these "risk management systems", which will now be closed systems, developed to confirm what is anticipated, but not to identify rare adverse effects in the long term. The definition of an "unexpected adverse effect" has moreover been purely and simply deleted from Article 1. And yet, the severe adverse effects of *thalidomide* and *DES* for example were entirely unexpected and were only discovered belatedly (3,4).

There are provisions for risk management plans and the protocols of accepted post-authorisation studies to be made public by means of an internet portal devoted to European pharmacovigilance (Article 101i). However, at the point when the authorisations are granted by the marketing authorisation committees, there are no provisions for publishing detailed requests for post-authorisation studies if it is deemed necessary on the grounds of suspected severe adverse effects, or the companies' responses, or the reasons for the withdrawal of the application after the firm has put forward its arguments (Article 101g). The companies' veto over pharmacovigilance data is such that publication of the executive summaries of post-authorisation studies can only take place with the consent of the firm, which can amend the data (Article 101g).

It is hard to see how these minimal demands and lack of transparency, with the industry allowed to intervene at every level of decision-making, can reliably protect European citizens (23). The prospect of the authorities maintaining a list of medicinal products under their intensive monitoring is not sufficiently reassuring (article 101i).

Post-authorisation studies are acknowledged by the European Commission itself as tools which are "*of poor quality and frequently promotional*" (1,24). And yet the Commission proposes to delete the provision requiring post-authorisation studies to be carried out in accordance with the requirements made on the granting of the marketing authorisation, thus opening up the way to abuse (**f**) (Article 1). Under the umbrella of risk management plans, there is a huge danger that the firms will circumvent the ban on direct-to-consumer communication on prescription drugs, or that they will attempt to create "loyalty" by signing patients up to so-called "compliance support" programmes, claiming they are informing patients about their medicinal products' risk-benefit balance (25).

Routine data gathering: centralisation and dilution. Various proposed arrangements alleviate the burden on the pharmaceutical companies, but to the detriment of patients' interests. For example, the companies will no longer be obliged to submit a detailed description of their pharmacovigilance system in support of their marketing authorisation application (Article 8), even though this provision makes it possible to check what means have been implemented, and facilitates contacts with the appropriate individuals and departments (**g**). Relaying pharmacovigilance responsibilities centrally to the holder of the marketing authorisation, the parent company, is likely to remove the responsibility from those marketing it at national level. It makes censorship easier and can slow down reporting.

The Commission's proposal for the way companies should record data does not allow for any external monitoring. They will not be under obligation to record reports they receive unless they "*consider that a causal relationship is at least a reasonable possibility*" (article 101e), and they need only submit a summary of the post-authorisation studies they have conducted to the authorities. Thus the companies will be acting as both judge and defendant and will have full latitude to manage pharmacovigilance data as they see fit.

It appears that the Eudravigilance centralised database for recording reports for the entire European Community is slowly being established (26). The conditions governing the recording and processing of data are unclear and responsibilities have not yet been clarified (**h**). We know only that the process is being driven by the recommendations of the International Conference on Harmonisation (ICH), developed in partnership with the pharmaceutical industry and the drug regulatory agencies (**i**). Eudravigilance remains a "black box" for European citizens.

The Commission plans for the European Pharmacovigilance Committee to oversee the implementation of good pharmacovigilance practice, the guidelines for pharmacovigilance management. The pervasive references to the ICH, which is heavily influenced by the pharmaceutical industry, give reason to fear that this "good practice" will result in the system being controlled by the companies at a more technical level (Article 101b) (**i**).

The long-awaited proposal to include direct reporting of adverse effects by patients is welcome. But it is unacceptable that patients should be asked to make their reports on intensively monitored drugs to the firms, as laid down in article 59. While it makes sense for the pharmaceutical companies to be involved in the collection of data on the adverse effects of their medicinal products and to pass their data on to the relevant authorities, the companies' pharmacovigilance systems must not under any circumstances replace national public pharmacovigilance systems (**j**). Each country's pharmacovigilance system makes it possible to produce a detailed analysis based on its expertise with regard to its population. Centralisation of all the reports at European level with no regional or national analysis is likely to result in a dilution of the data, which will be impossible to interpret, rendering the database useless.

Alerts: confusion of roles. As regards the European Medicines Agency monitoring the information held in the Eudravigilance database, it is envisaged that warning signals will be passed on to the pharmaceutical companies, to the European Commission and to the member states, but not for these to be made public, depriving inde- ►►

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f- *The authorities do have the opportunity to signal their objections to the draft protocol proposed by the firm, but only within 60 days of the submission, whereas they must submit detailed grounds for their objections in writing (article 101 h).*

g- *It will be sufficient for the qualified person responsible for pharmacovigilance in a given company to sign a statement to the effect that his/her employer has the necessary means to fulfil their tasks and responsibilities (article 8). The Pharmacovigilance System Master File should be made available to the authorities on request, or can subsequently be consulted during an inspection, but it will not be routinely controlled (Article 8.3). For authorisations obtained through the centralised procedure, the pharmacovigilance authority responsible will be that of the country of residence of the person responsible for pharmacovigilance of the holder of the marketing authorisation, giving the firms the freedom to choose the country with the least stringent demands and penalties in the event of non compliance.*

h- *EMEA's 2006 Annual Report lists 283,768 adverse drug reaction reports put into the Eudravigilance database in 2006 (ref 34) but the patients and caregivers, who do not have access to it, see almost nothing of these reports (ref 35).*

i- *The aim of the ICH (International Conference on Harmonisation), a process implemented since 1990 on the initiative of the US, European and Japanese regulatory authorities and pharmaceutical industries, is to harmonise the authorisation procedures for medicinal products. In practice, the work of the ICH committee often leads to a levelling down, especially with regard to pre-authorisation evaluation and pharmacovigilance, with the adoption of recommendations often based on minimal requirements (ref 14).*

j- *Patients' reports must be reported to the authorities of the member states. The proposal in Article 101e refers in particular to their websites, but makes no mention of the regional pharmacovigilance centres which have been set up in several countries, even though their importance, due to their proximity to those reporting, was underlined in the report published in 2006 (ref 19).*

► pendent organisations of valuable information (Article 101d).

Data-mining software, which is supposed to facilitate the detection of pharmacovigilance signals within the Eudravigilance database using statistical methods, was tested in 2007 (26). But tangible results for patients still remain to be seen: too many medicinal products with a negative risk-benefit balance, undetected by this type of automated method, are still available on the European market (27).

The Commission proposes to subcontract the monitoring of "*all available relevant data including data on Eudravigilance for signals of new or changing risks (…)*" to the pharmaceutical companies, even though they are judge and defendant (Section 7.4.(d); article 101l). It will also be up to the firms to alert the authorities in the event of new data likely to affect their medicinal product's risk-benefit balance (Article 101h).

Data analysis: dilution and secrecy. Once the alert has been given, the relevant pharmacovigilance data can be gathered for analysis (reports filed on Eudravigilance, detailed results of post-authorisation studies, periodic safety update reports, etc.).

Access to anonymous individual reports is still difficult for members of the public and independent bodies: they "*may be requested by the public*" and these data shall be provided "*within 90 days (…)*" (Article 101d). And yet, given that these data derive from spontaneous reports, they belong to the community (**k**).

Concerning the results of post-authorisation studies, it is up to the companies, acting both as judge and defendant to: "*consider whether the results of the study impact on the product labelling*" (article 101h.1.i) or "*might influence the risk-benefit balance of the medicinal product*" (Article 101h.1.g).

The European Agency is also supposed to entrust the exploitation of these data to the pharmacovigilance centre of the World Health Organisation (WHO) in Uppsala, which has come under considerable criticism for its lack of transparency (28,29) (Article 101m).

Subcontracting the interpretation of the data to the pharmaceutical companies and the WHO Collaborating Centre deprives the member state Agencies of their role and does not enable them to strengthen their competencies, which makes them even more reliant on the firms.

On the pretext of "rationalising" the system, the Commission proposes changes to the frequency of Periodic Safety Update Reports (PSURs) provided by the companies to the authorities according to "*knowledge about the safety of the product*" (**l**) (article 101f). This provision effectively means abolishing the long-term monitoring of adverse effects, for example: "*no PSURs for old established products*" (section 3.2.7 of Introduction). And yet, there are examples of adverse effects which have sometimes taken more than 30 years for the relationship between cause and effect to be established. These effects can sometimes be very severe, for example teratogenic effects (*thalidomide*, *DES*, etc.) or carcinogenic effects (*DES*) (3,4). There are no provisions for the PSURs to be made public whereas they ought be so already, in accordance with Regulation (EC) 1049/2001 regarding public access to European Parliament, Council and Commission documents, since these are Commission documents. There are only provisions for the conclusions of the PSUR assessments by the member state chosen as rapporteur to be made public (article 101f) (**m**). Under such conditions, how can we accept the reasons given for the authorities' decisions and the arguments on which they are based?

Decision-making process: the payer decides. At present, the prevarication and slowness of the pharmacovigilance decision process leaves patients exposed for too long to the harms of drugs with a negative risk-benefit balance (14). This delay can chiefly be explained by the fact that since the pharmacovigilance authorities' recommendations are non-binding, they are not sufficiently heeded by the European and national marketing authorisation committees when it comes to amending or withdrawing marketing authorisations. The marketing authorisation committees have both an in-built conflict of interests: acknowledging the need to take these measures is tantamount to admitting that they had made a poor decision in approving the product in the first place; and a conflict of interest with the pharmaceutical companies, their priority "customers" (**n**).

The 2004 legislation strengthened the resources to be devoted to pharmacovigilance, insisting that it should be publicly funded to guarantee its independence (**o**), specifying that: "*Activities relating to pharmacovigilance, (…) shall receive adequate public funding commensurate with the tasks conferred*" (Article 67.4 of Regulation 726/2004 (EC)). The Commission is planning to abolish this requirement for adequate public funding by adding to the existing provisions that these funds "*do not preclude the collection of fees charged to marketing authorisation applicants or marketing authorisation holders for these activities*" [Editor's note: i.e. pharmacovigilance] (Article 101c). The funding of pharmacovigilance will therefore be directly dependent on the number of marketing authorisations granted by the national agencies.

The Commission's proposed renaming of the "Pharmacovigilance working party" (PhVWP) as the European Committee on Pharmacovigilance is merely a smokescreen: its role is still limited to producing "recommendations" which are not sufficient for withdrawing or amending a marketing authorisation without a further recommendation by the marketing authorisation committee (Committee for Medicinal Products for Human Use at EU level) (article 101k.9).

Concerning evaluation at EU level, the results of which are applicable to all the member states, only the authority's final decision will be made public (article 101k.10). However, article 126b of Directive 2004/27/EC relating to the authorities' obligations regarding transparency stipulates that the competent authority shall "*make publicly accessible (...) records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions*". Similarly, the inspection reports, especially in the event of a firm's failure to fulfil its obligations should be made public, together with the penalties imposed. There are no such provisions in the Commission's proposals (article 111).

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k- *In some countries, the Netherlands and the UK in particular, data on adverse effects are readily accessible (ref 40).*

l- *Currently, the pharmaceutical companies are obliged to provide Periodic Safety Update Reports to the authorities, containing a scientific evaluation of their medicinal product's risk-benefit balance, every 6 months for the first 2 years of commercialisation, once a year for the next 2 years, then every 3 years (Article 104.6 of Directive 2004/27/EC and Article 24.3 of Regulation 726/2004(EC)). In practice, the fulfilment of this obligation is poorly monitored (ref 39). The Commission provides for firms to be allowed to change this frequency, even though these provisions were required for obtaining a marketing authorisation (article 101 f).*

m- *Progress needs to be made in stamping out the hypocrisy of "trade secrets" in relation to consumption data (Article 101.i.6). This information is sold to the firms by companies specialising in the sale of economic data. The Commission acknowledges in its proposals that consumption data are of major public health interest: being aware of the size of the population likely to be exposed to an adverse effect is a necessary factor for establishing the risk-benefit balance (Articles 101f and 101k.8).*

n- *The funding of regulatory agencies chiefly from fees paid by the firms for examining marketing applications reduces them to the rank of service providers to the firms. The granting of marketing authorisations through the mutual recognition procedure leads to cronyism, the agencies being placed in a competition with each other by the firms (ref. 12).*

o- *"The management of funds intended for activities connected with pharmacovigilance (...) shall be under the permanent control of the competent authorities in order to guarantee their independence." (…) (Article 102a of Directive 2004/27/CE).*

Information on adverse effects: blurring of roles. It is the responsibility of the authorities (European and national drug regulatory agencies, regional pharmacovigilance centres, etc.) to process and interpret the data, and then to communicate the results. And yet, at present, the dissemination of "Dear Doctor" letters is handled by the pharmaceutical companies, which is symptomatic of the blurring of roles. This practice sees the companies speaking on behalf of the regulatory agencies, and is likely to result in abuses with companies delivering information of promotional nature (**p**).

To make patients aware of a medicinal product's adverse effects, the proposal to include a box on the patient leaflet highlighting some "key safety information" is not sufficient and seems even counterproductive (Article 11). This is a case of "the trees hiding the wood", with the information in the box focusing patients' attention on the few known adverse effects. Furthermore, this information is likely to be confused with the firms' advice on "risk minimisation" when adverse effects occur. Is the priority to help patients to cope with a drug that turns out to have severe adverse effects, even when there are alternative therapies available? It is certainly best to encourage patients to review their treatment with the healthcare professionals and choose one with a better risk-benefit balance.

To help identify recent pharmacovigilance decisions, a complete presentation of the product's adverse effects is preferable, drawing attention to the most recent warnings by printing this information in bold on the patient leaflet.

Concrete proposals for strengthening pharmacovigilance in Europe effectively

To strengthen pharmacovigilance in Europe effectively requires changing marketing authorisation criteria by encouraging better quality evaluation, promoting increased transparency, clarifying the respective roles of the authorities and the companies and putting in place the resources for an effective pharmacovigilance system.

More stringent marketing authorisation criteria. The vast majority of new drugs currently coming onto the market do not offer any real therapeutic benefits, and can even be regressive, needlessly exposing patients to adverse effects (7). The authorities do not require pharmaceutical companies to demonstrate that their new drug offers "added therapeutic value" compared with those already on the market as part of the authorisation process, even in fields where there are already numerous, acceptable, well-established drugs for the same indication (30). The entire population is therefore being exposed irresponsibly to the harms of new drugs whose balance of risks and benefits is not properly established, and which becomes unfavourable the moment an adverse effect occurs if the efficacy is not demonstrated. With the Commission's proposals, a new medicinal product's effectiveness is no longer even a criterion for obtaining a marketing authorisation!

The marketing authorisation criteria should be made more stringent to give patients and the community more robust guarantees. Insisting that a new drug must represent a therapeutic advance would avoid needlessly exposing the population to preventable harm (30). This seems to be the only proposal capable of channelling research towards fields where patients lack effective treatments. It is an efficient way of halting the present waste where member states' health budgets are funding, at high prices, regressive treatments and useless new drugs.

Increase transparency. The improved regulations relating to the authorities' transparency introduced in 2004 should be applied more rigorously, and strengthened. There are several measures which are simple to implement:
– help build a true profile of medicinal products' adverse effects and recent pharmacovigilance decisions;
– help identify drugs that have been authorised despite insufficient evaluation, by drawing on article 54 which states that "*all suspected adverse reactions should be reported (see leaflet for details)*", and also using the pictogram already used widely in Europe of a black triangle pointing downwards (▼) next to the brand name on each packet and on the primary packaging;
– give the public access to pharmacovigilance information: Periodic Safety Update Reports (PSURs) including consumption data; complete PSUR evaluation reports; access to Eudravigilance reports and to a periodic summary of Eudravigilance reports which the EMEA should be obliged to produce; requests for post-authorisation studies or for the setting up of risk management plans together with the firms' responses;
– make public the detailed reasons behind pharmacovigilance decisions.

Give the authorities the means to be independent from pharmaceutical companies. It is essential for the authorities to be financially and intellectually independent from the pharmaceutical companies.

A key provision of the 2004 legislation is that activities relating to pharmacovigilance should receive adequate public funding commensurate with the tasks conferred. This must be maintained and finally applied (67.4 of Regulation 726/2004 (EC)).

Developing the authorities' intellectual independence from the firms involves re-assessing the position of the International Conference on Harmonisation (ICH) in the drafting of regulatory guidelines on medicinal products. Healthcare actors must systematically be called upon to provide input by means of public consultations, including consultations on the "standards" drawn up by the ICH and perceived as "enforceable" by some agencies and the EU authorities. And their input must be taken fully into account.

Providing the means for an effective public pharmacovigilance system. An effective pharmacovigilance system requires significant public funding and a genuine political will. The priorities are:
– to give the European Committee on Pharmacovigilance the authority to impose modifications to patient information leaflets or the withdrawal of products with an unfavourable risk-benefit balance;
– to collect reports of adverse effects by the public and exploit this information efficiently, making it accessible to all European citizens once names have been removed;
– to control post-market studies, which must be conducted by independent teams;
– to opt for cooperation and dialogue over a monopoly with centralised information on drug safety. By consulting medication errors reporting programmes more systematically, the agencies would benefit from additional analyses and expertise, in the best interest of patients;
– to have the power to impose real penalties on firms that do not fulfil their obligations (the proposal in Article 101o is evasive) (**q**). ►►

p- For example, the French regulatory agency had to ban, after the event, a letter featuring celecoxib distributed by the firm which, instead of carrying the expected warnings, was tantamount to an advertisement boasting of this drug's safety compared with rofecoxib which was withdrawn from the market (ref 37).

q- An EU Regulation in 2007 laid down the penalties to be applied in the event of infringement of some obligations (ref 38).

► With marketing authorisations being granted more easily and sooner, and a system that makes it possible to hush up emerging pharmacovigilance cases – at least until firms have earned the anticipated "return on their investment", the European Commission hopes to help boost the pharmaceutical companies' competitiveness.

In actual fact, the European Commission is surrendering its mission to protect European citizens (Article 125 of the Treaty establishing the European Community) in favour of protecting the short-term financial interests of the pharmaceutical companies.

Medicines in Europe Forum, ISDB and HAI Europe call on the Commission to re-focus its efforts and defend the public interest.

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