Brussels, 15 September 2012
Joint answer

European Medicines Agency and pharmacovigilance: no to a fee-for-service system

Summary

On 18 June 2012, the EU Commission published a draft concept paper for public consultation on the "Introduction of fees to be charged by the European Medicines Agency for pharmacovigilance" (1). Regrettably, the European Medicines Agency (EMA) is being turned into a mere provider of services to the pharmaceutical industry. Other strategies for funding that would help drug regulatory agencies to be more independent do exist. They should be carefully considered.

Foreword

Earlier this year, the EU Commission issued a draft concept paper for public consultation on the "Introduction of fees to be charged by the EMA for pharmacovigilance" (1). The *Medicines in Europe Forum* (MiEF) welcomes the opportunity to respond to this public consultation and would like to highlight particularly worrying elements of the document.

In 2004, in recognition of the public interest in pharmacovigilance, European Regulation (EC) 726/2004 recognized the need for pharmacovigilance to remain independent, and established provisions for it to be publicly funded : "*activities relating to pharmacovigilance* (...) *shall receive adequate public funding commensurate with the tasks conferred*" *(article 67(4)).*

A clear lack of political will has prevented this provision from being implemented in practice. Most notably, in its legislative proposals on pharmacovigilance published in December 2008, the EU Commission proposed a fee-for-service system, whereby the EMA would charge fees to industry in exchange for post-marketing surveillance activities. The new pharmacovigilance legislation (Regulation (EU) No 1235/2010), adopted in 2010, includes this provision, ending the public funding requirement.

Health authorities' resources in pharmacovigilance need to be strengthened. Yet charging pharmaceutical companies fees, as the draft concept paper proposes, could have perverse effects, and these should not be underestimated.

Rather than responding to the ten consultation items, our response rests on a principle to safeguard: the independence of drug regulatory agencies from the pharmaceutical industry - a prerequisite to ensure the agencies' accountability to European citizens.

If indeed the aim is to reinforce pharmacovigilance in Europe, then alternative sources of funding – other than a fee-for-service system – must be considered. We propose further options for pharmacovigilance activities' funding on pages 4 and 5.

Fees undermine the independence of drug regulatory agencies

Since its creation in 1995, revenue for the European Medicines Agency (EMA) has increasingly been derived from fees charged to the pharmaceutical industry. For 2012, fees from industry are forecast to account for "*approximately 85% of EMA's revenues (…), and the remaining 15% from the EU budget*" (1). The danger is that drug regulatory ruthorities become service providers for pharmaceutical companies, at the expense of their public health mandate.

Pre-marketing: drug licensing fees have detrimental effects. Evidence from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) illustrates the detrimental effect of a fee-for-service mechanism:

- In the US, within the framework of PDUFA (**a**), strict timelines must be adhered to by FDA officers when assessing new drugs, thus undermining the quality of their work (2). This has led to an unprecedented number of drug withdrawals for safety reasons (3). Public Citizen - a consumer watchdog group that has monitored FDA's work for more than 40 years, explains that "*with the agency continually looking over its shoulder so as not to endanger its funding stream (…), there has been a fundamental change in the atmosphere within the agency such that pharmaceutical companies are increasingly seen as stakeholders, customers or even clients*" (2).
- Recently, concerns about potential conflicts of interest at the highest level of the EMA management have led Members of the European Parliament to refuse to approve the Agency's accounts for 2010 and 2011 (4).

By paying a fee when submitting a new drug for assessment, or by requesting paid scientific advice (**b**), pharmaceutical companies are gradually increasing their influence on the decision process.

Post-marketing surveillance: extending the fee-for-service system is dangerous. Adverse drug reactions are a sensitive issue (read on page 3). Many European Member States therefore made pragmatic choices aimed at safeguarding competent authorities' independence. In France, the *benfluorex* (Mediator°) disaster triggered new legislation and, since December 2011, the French National Agency is entirely publicly funded by the Ministry of Health. In Germany, this "de-linking of money" exists since 2003: the drug licensing fees are paid to the State, and the Drug Regulatory Agency (BfArM) is 100% funded by the State budget (5). Across Europe there are many competent authorities (i.e. Health Technology Assessment (HTA) bodies, Pharmacovigilance Centres) that are largely publicly funded.

At the European level, according to the new pharmacovigilance legislation, drug regulatory agencies have to submit any safety measure they intend to take to the pharmaceutical company concerned (e.g. a requirement to conduct a post-authorisation study as a condition to the marketing authorisation). Pharmaceutical companies then have the "right" to argue against the proposed measure (*articles 22a of Directive 2010/84/EU*). The problem is that these bilateral exchanges between companies and agencies are not made public. In the end, should the measure not be implemented, the public knows nothing of the drug regulatory agency's safety concerns and the public remains unaware of the arguments used to prevent the measure's implementation. What can we expect next: confidential meetings between industry and EMA staff to discuss whether or not the agency can release a drug safety warning to the public?

Fees make drug regulatory agencies dependent on funding from the industry that they are supposed to be regulating. This is an insurmountable conflict of interest.

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a- Since the first Prescription Drug User Fee Act (PDUFA) was passed in 1992, the US Food and Drug Administration is allowed to collect fees from pharmaceutical companies, notably to fund the new drug approval process. The user fees have required the establishment of deadlines leaving the FDA with little flexibility (ref. 2).

b- Requesting paid scientific advice makes health authorities become co-developers of the products they will eventually assess…

EMA's pharmacovigilance activities: first and foremost a service to citizens

The aim of pharmacovigilance, as a scientific discipline, is to detect adverse drug reactions signals as early as possible to help heath authorities to make timely decisions, in order to protect public health. Pharmacovigilance decisions, such as the suspension or withdrawal of a marketing authorisation due to a negative harm-benefit balance, can adversely impact product sales. Health authorities' pharmacovigilance activities are first and foremost a public-interest service.

However, the European Commission's draft concept paper states that "*the activity of the regulatory authorities in the area of pharmacovigilance (…) constitutes a service to the industry*"... and foresees that regulatory authorities actually serve industry first, even if it is at the expense of European public health.

Crucial pharmacovigilance activities are not funded. The failure to make timely decisions, as in the case of *rofecoxib* (Vioxx°), or *rosiglitazone* (Avandia°) (6), demonstrates that EMA's pharmacovigilance activities and resources must be strengthened. **It is particularly necessary to increase the EMA's and National Competent Authorities' capacity to independently collect and analyse adverse drug reactions reports made directly by health professionals and patients.**

There is ample evidence that pharmaceutical companies often withhold data to delay pharmacovigilance decisions that would otherwise adversely affect sales (**c**). Two examples reported in the media in the summer of 2012 remind us that it is irresponsible to expect pharmaceutical companies to admit the adverse reactions due to the products they sell (**d**).

Unfortunately, the new pharmacovigilance legislation foresees a stronger role for the industry in the collection and analysis of pharmacovigilance data, literally letting the fox guard the hen house (7). Drug regulatory agencies will be bound to base decisions on information that companies have already interpreted for them. This arrangement provides ample opportunities for pharmaceutical companies to withhold and manipulate data.

Several fees are envisaged in the draft concept paper, most notably for the procedures involving assessments by the Pharmacovigilance Risk Assessment Committee (PRAC):

- A fee for assessments of Periodic Safety Update Reports (PSUR);
- A fee for assessment of Post-Authorisation Safety Studies (PASS).

A ridiculously low pharmacovigilance service fee (maximum 1 000 euros per year and per medicinal product, with exemptions) is being considered for reviewing the literature, and keeping the ADR database up-to-date. This pharmacovigilance service fee should also be used to cover additional activities of public interest such as the organisation of pharmacovigilance public hearings (*implementation of article 107j of Directive 2010/84/EU*). Remarkably, the European Commission seems to have forgotten these costs.

Ultimately, the most useful pharmacovigilance activities to be performed by drug regulatory agencies, i.e. the collection and analysis of data, will remain underfunded. This will probably reorient EMA's focus towards activities less likely to lead to decisions that could adversely affect sales: PSUR and PASS assessments are in fact largely based on data interpreted by companies, biasing the conclusions and preventing thorough independent analysis.

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c- Law suits in the US have granted access to pharmaceutical companies' internal memos. They show that, very often, pharmaceutical companies are aware of their medicines' adverse effects, but attempt to conceal them from the public as long as possible. For example, in 2007, Lilly paid out several tens of thousands of dollars to each of the 28 000 plaintiffs in the US who accused the company of misinformation about the adverse effects of the neuroleptic drug *olanzapine* (Zyprexa°), which causes diabetes and significant metabolic disorders. These safety concerns were known to the company. Another example: pharmacovigilance data (increased suicide risk) relating to the use of *paroxetine* (Deroxat°/Seroxat°) in children was proven to have been withheld by GlaxoSmithKline.

d- GlaxoSmithKline pleaded guilty and agreed to pay 3 billion dollars, a record fine, to end several court cases filed by the US Health Authorities, notably for failure to provide clinical data regarding cardiovascular safety of the diabetes drug Avandia to the Food & Drug Administration in its required periodic reports (ref. 11). In 2012, a routine inspection by the EMA revealed that Roche had failed to report to the agency a total of more than 80 000 adverse reaction reports caused by their products, out of which 15.000 were fatal events. (ref.12).

A perverse incentive in pharmacovigilance referrals: principled companies will be penalised. A referral is a procedure used to resolve disagreements and to address concerns about the risks for public health of a medicine or a therapeutic class. The EMA is then requested to conduct a scientific assessment of a particular medicine or therapeutic class on behalf of the European Union. At the end of the referral, the Committee for Medicinal Products for Human Use (CHMP) makes a recommendation for a harmonised position across the EU to the European Commission. The European Commission then issues a decision to all Member States reflecting the measures to be taken to implement the CHMP recommendation.

In the draft concept paper, charging a pharmacovigilance referral fee is proposed for:

- Referrals that are triggered when a Member State varies, suspends or revokes a marketing authorisation for a medicine in its territory due to a safety issue (*Article 107 of the Directive*) - cost from 80,300 to 267,400 euros (maximum);
- Referrals "*which relate to the assessment of specific parts of the marketing authorisation, e.g. introduction of new contraindications*" (changes usually introduced via Type II variations) – cost - 80,300 euros.

These pharmacovigilance referrals fees can have perverse effects:

- with referrals triggered by a Member State because of a safety issue, asking a pharmaceutical company to pay for the re-assessment of its product is particularly dangerous because the assessment is likely to adversely affect its sales. To make their scientific evaluation, drug regulatory agencies should be totally objective and not act as a service provider to their payer, who happens to be the party with a vested interest;
- with referrals relating to the assessment of specific parts of the marketing authorisation for safety reasons, charging referral fees means that principled marketing authorisation holders, who routinely and proactively share their safety concerns with drug regulatory agencies, will be penalized for giving drug regulatory agencies "extra work"! This could dissuade marketing authorisation holders from reporting such concerns. Such a framework could be seen as providing incentives for marketing authorisation holders to dilute or underestimate the clinical consequences of their products' ADR reports, thus preventing new contraindications from being added or costly changes to the marketing authorisation from being made.

Referrals for safety reasons are a major public health issue. One that is serious enough to justify:
- the allocation of public funds through the EU budget to support the independence of drug regulatory agencies;
- timely decision-making considering that the doubt should benefit the patients (precautionary principle).

Funding EMA's pharmacovigilance activities: concrete alternatives

Health authorities have a responsibility to act objectively and in the public interest, without being swayed by the business concerns of companies who are seeking product approval or who are "regular clients" in the framework of post-marketing follow-up.

Activities undertaken in the public interest demand and deserve adequate public funding. If political will to publicly fund pharmacovigilance activities is insufficient, several alternatives are possible. Health authorities' pharmacovigilance activities can be funded by: introducing a levy on the volume of sales; redirecting a percentage of the promotional expenses, or introducing a tax based on defined daily dose or unit of outer packaging (box), etc.

Public funding: common investment, common benefit. Public authorities are accountable for protecting public health. Since they also are responsible for granting marketing authorisations, they need to carry out pharmacovigilance activities to prompt timely public health decision-making.

Public funding of health authorities' pharmacovigilance activities should be considered a societal investment, most particularly by considering the savings to be made from a well-functioning detection and evaluation system: a decrease in adverse drug reactions means a reduction in hospitalisations, in suffering, in morbidity, in mortality, of days absent from work and in medical consultations.

A percentage of sales turnover to support a global pharmacovigilance fund. Another option is to increase the pharmacovigilance service fee so that it will cover all pharmacovigilance activities by health authorities. Pharmaceutical companies would be required to pay a percentage of their sales (global turnover) to support a global pharmacovigilance fund. Health authorities would then be free to decide how much of that money to spend on adverse drug reactions collection and analysis, on PSUR and PASS assessments, etc. Such a scheme would provide drug regulatory agencies with greater independence, rather than having fees paid in exchange for the provision of specific services to pharmaceutical companies. This measure would also be more equitable for marketing authorisation holders than rather arbitrary fee incentives for micro, small and medium-sized enterprises.

A percentage of promotional spending as part of the pharmacovigilance service fee fund. Pharmaceutical companies spend on average 25% of global turnover in promotional activities (8,9). Promotional activities by definition aim to increase sales. Aggressive promotional activities come into play when a medicine is less effective and/or has a worse safety profile than a competitor for the same therapeutic use. By increasing sales, promotional activities also increase the likelihood of ADR occurrence. From a public health perspective, it would make sense to require pharmaceutical companies to pay a percentage of their promotion budget to support a global pharmacovigilance fund. This should not however be the only source of funds in order to prevent health authorities from becoming dependent on the volume of companies' promotional activities. This percentage of promotional spending could be part of the pharmacovigilance service fee, in addition to either public funds or to funds obtained from the levy on the percentage of sales (global sales turnover).

A tax per defined daily dose or a tax per outer packaging (box) requested from all actors in a medicine's distribution chain. According to the "inverse benefit law", "*the more widely drugs are marketed, the more diluted become their benefits but the more widespread their risks of harm*" (10). That is a good argument in favour of another type of tax: a very small amount of money could be requested from all actors in a medicine's distribution chain to support a pharmacovigilance fund. This amount could be calculated per defined daily dose or per outer packaging (number of boxes of a medicine sold). This innovative solution has been adopted in Belgium (prescribers are exempted, although it would have reminded them of ADR risks due to irrational prescribing). In line with the Belgian law passed in March 2012, pharmacists will pay a contribution of 0,00596 euro for each package of an authorised medicine dispensed; wholesalers pay a contribution of 0,00014 euro for each package of an authorised medicine distributed; marketing authorisation holders have to pay a contribution of 0,01118 euro for each package of an authorised medicine put on the market (except if centrally authorised) as well as a standard fee of 58 euros per medicine authorised to be marketed by the Belgian Health Ministry, in addition to 58 euros per medicine admitted for reimbursement, and 58 euros per medicine authorised for parallel import (11).

The European Medicines Agency (EMA) should not be turned into a mere provider of services to the pharmaceutical industry. Other strategies should be considered for funding pharmacovigilance activities that would help drug regulatory agencies to be more independent.

Medicines in Europe Forum **HAI Europe** **ISDB**

Annex

Additional comments on:

- **the concept of grouping**
- **the fee incentives for micro, small and medium-sized enterprises**
- **an adequate financing structure for patient and consumer involvement in the PRAC**

Grouping of several marketing authorisation holders (MAH) for the purpose of paying a single fee. The grouping of several marketing authorisation holders (MAH) of products containing the same substances would allow them to pay a single fee. This measure would reduce the number of assessments to be carried out by drug regulatory agencies.

Yet, this proposal raises quite a number of concerns:

- In PSURs, MAHs have to produce their medicine's "*scientific evaluation of the risk-benefit balance*. Who is then responsible should ADRs be dissimulated or incorrectly analysed or interpreted?
- A medicine's formulation, administration route, packaging are important issues to take into account when assessing its safety. For example, evidence indicates that well-designed packaging improves patient safety, while poorly-designed packaging generates medication errors (12). Packaging quality should be systematically assessed as part of the PSURs, PASS, and risk minimisation measures, etc. Often, for the same medicine, there is no unique pharmaceutical form and packaging across all Member States of the European Union, and therapeutic indications may differ from country to country. In practice, will it be possible to assess all the packages at the same time and to account for different therapeutic indications?

Fee incentives for micro, small and medium-sized enterprises. Another approach that could be more equitable and make more sense in terms of social responsibility would be to require that a percentage of sales turnover be paid to the EMA in order to fund pharmacovigilance activities.

Insufficient financial support for representatives of medicines users on the PRAC. The new pharmacovigilance legislation foresees the inclusion of one patient representative in the Pharmacovigilance Assessment Risk Committee (PRAC). Involvement of patients and consumers in pharmacovigilance activities is important to foster decisions which give the benefit of the doubt to patients in case of safety concerns, in line with the precautionary principle. Although the patients' representative sustenance costs will be covered, there is no financial compensation foreseen to offset the time costs of: participating in monthly four-day PRAC meetings in London, reviewing documents and preparing for the PRAC meetings, developing and maintaining technical expertise in the field of pharmacovigilance. This underfunding of patients' representative pharmacovigilance activities leave many potential representatives unable to perform this function as part of their regular employment. In order to attract patient and consumer representatives who are independent of funding from the pharmaceutical industry, any pharmacovigilance financing structure must take better account of the financial implications for patient and consumer representatives and provide adequate support for civil society involvement.

Short presentation of the signatory organisations

ISDB. The International Society of Drug Bulletins, founded in 1986, is a worldwide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently ISDB has around 80 members in 41 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org

MiEF. The Medicines in Europe Forum (MiEF) was launched in March 2002 and reaches 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. It is a unique group and a testament of the importance of European medicines policy. Contact: pierrechirac@aol.com

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 their rational use. More info: www.haieurope.org. Contact: katrina@haieurope.org

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