Response to European Commission Public Consultation: An assessment of the Community System of Pharmacovigilance

We are writing as an *ad hoc* group of pharmacoepidemiologists from several EU countries to put forward broad and long-term proposals for strengthening the Community pharmacovigilance system.

During the last ten years a lot of progress has been made in terms of co-operation between Member States and organising the regulatory system. Although there are important issues to be faced in respect of further development in these areas, we do not anticipate that they are likely to be critical to the success of the public health objective of pharmacovigilance. Therefore, although we agree with some aspects of the core recommendations of the Fraunhofer Institute report, we do not believe they go far enough or that implementing them would be likely to produce major gains. In our view, the principal focus should be on three areas, as follows:

(1) Development of the methodologies and science base
(2) Stronger regulation in the post-authorisation period
(3) Education

Development of the methodologies and science base

Pharmacoepidemiology is a relatively young discipline. In twenty years it has been developed from scratch and is now recognised to be of considerable importance as a tool for the evaluation of the safety of medicines. Nevertheless we believe that important advances in the data resources and methodologies are needed, and are potentially achievable, provided resources can be devoted specifically to this purpose. Progress in this respect is critically dependent on data resources and, looking at all the resource now going into pharmacovigilance, we would question the current balance of inputs between spontaneous adverse drug reaction (ADR) reporting systems and other methods. We would like to stress that we recognise the need for and value of such systems but would argue that far too much of the available resource is being channelled in this direction, primarily as a result of regulatory requirements on the pharmaceutical industry. The sending of an ADR report from A to B confers no public health benefit *per se* but is probably the single biggest driver of the current Community system. Not only should the Commission be striving to ensure that the whole spontaneous reporting system becomes much more efficient, they must then find ways to ensure that resources freed up are used for safety purposes and redirected towards higher levels in the evidence hierarchy. Ultimately, the main way in which pharmacovigilance could be improved would be by generating better data more quickly in the post-authorisation period. Achieving this will require development of new pharmacoepidemiology initiatives in the EU and more effective collaboration between existing ones. Movement towards these goals will need to be driven largely by governments rather than the pharmaceutical industry.

Stronger regulation in the post-authorisation period

Prior to the granting of a marketing authorisation, EU regulators have very major powers to specify the data that they require and pharmaceutical companies have a

large incentive to meet these demands. In general terms, we believe that this part of the system operates well. Once an authorisation is granted, the situation is different and companies have much greater scope for contesting regulatory requests, primarily because the powers available to the authorities are insufficient or inappropriate to the particular circumstances. Paradoxically, the ability to remove the marketing authorisation is normally of little use because it is too draconian for most situations. Regulators are also reluctant to use it because it will disadvantage some patients who are already using the medicine. The practical consequence is that companies may delay or not initiate essential safety studies, including those to which they may have made a prior commitment. In these circumstances regulators lack the necessary powers of enforcement and the Commission should initiate the development of legislation to rectify this deficiency.

In the last few years there has been one potentially very important development in this field that is now a legal requirement in the EU underpinned by guidance i.e. risk management plans. We are convinced that this approach represents a potential major advance. In practice, however, there is a very real danger that it could become a paper exercise that consumes more resource for little public health gain. Input from pharmacoepidemiologists is likely to be critical to this process but we have seen little evidence of their involvement so far. The original vision that these documents would become publicly available at the time of authorisation seems to have been forgotten and with it a major opportunity to increase public confidence is being lost.

The most important post-marketing safety issue of the last few years, i.e. the cardiovascular safety of coxibs illustrates well the issues we have raised above. It is also one of several recent safety issues (SSRIs and suicidal thoughts in children and stroke with atypical antipsychotics are two others) that highlight the potential impact of clinical trials and overviews on safety evaluation after marketing authorisations have been granted. In this regard there seems to be a gap in the regulatory scrutiny of safety data. The only times regulatory authorities are provided with all the available safety information from clinical trials is with the marketing authorisation application or if they make a specific request because of concerns arising from other data. Yet such data continue to be generated and may only be submitted to the authorities if the company perceives there to be a safety problem or applies for an extension to the authorisation. We welcome the initiative to make clinical trial data publicly available but would ask – who will be systematically scrutinising the whole picture on an ongoing basis? Our view is that this should be a regulatory task – it is a new one and requires additional powers and resources.

An important element of the whole regulatory and risk management process that has been largely ignored is the development of valid measures of success. This should be an important research priority and ultimately lead to more effective regulation.

Education

Other than the regulatory system, we recognise that many other aspects of the health care system impact on the safe use of medicines. These systems vary considerably between Member States but, in general, closer integration with other healthcare safety systems seems desirable. This underlines the value of national or regional drug utilisation data, the potential value of which seems yet to be fully recognised. Whilst

the organisation of regulation at the EU level has some advantages, it also means that it is more remote from everyday practice. Effective pharmacovigilance depends on engaging healthcare professionals and much more needs to be done in this respect in terms of education. In the EU, training programmes in pharmacopidemiology lag behind those in North America and need to be fostered.

Responsibilities within the Commission

The main driver for setting up the EU regulatory system for pharmaceuticals has been related to the single market. Whilst this seems to have been achieved without losses in respect of the public health objective, real gains have yet to be made. We applaud the Commission's desire to improve the pharmacovigilance system but we doubt that fundamental change will happen without now introducing clear organisational separation of the single market and public health objectives of the system. In practice, this means transferring the responsibility for the regulatory system to the Directorate General for Health.

Summary of our broad recommendations to the Commission

1. Move the responsibility for the pharmaceutical regulation into the Directorate General for Health with the aim of furthering its public health goals and, specifically, improving pharmacovigilance and its integration within healthcare systems.
2. Initiate a program designed to provide a single highly efficient spontaneous reporting system for the EU within five years, with the consequence of reducing the burden of regulatory reporting on the industry for equal public health gain and freeing resources for pharmacoepidemiological studies
3. Initiate a review of pharmacoepidemiology for the purposes of considering how advances in data resources and methodologies can be rapidly promoted within the EU; how to promote collaboration between EU initiatives in pharmacoepidemiological research; and how to foster the development of educational opportunities in the discipline.
4. Fund ongoing research into the public health burden of adverse drug reactions within the EU; their prevention through building a wider safety culture in relation to use of medicines; and the development of valid indicators of the success or failure of risk management activities.
5. Further develop regulatory legislation relating to the post-authorisation period in order to ensure that:
    - Risk management plans can be enforced such that companies are obliged to perform pharmacoepidemiological studies designed to provide timely, high quality safety data.
    - Appropriate powers that do not disadvantage users of medicines are available to act against companies who fail to deliver on risk management plans.
    - All risk management plans will be made publicly available once an authorisation has been granted.
    - Companies are obliged to provide regulators with safety data from all post-authorisation studies, including clinical trials and that regulators are obliged to scrutinise it.

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These are our collective personal views and do not necessarily represent those of any organisations with which we are associated.