

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

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## ***Executive summary***

The regulation of the input and collation of data and information in pharmacovigilance has added considerable rigour to the discipline. The next needs of pharmacovigilance are summarised below:

- A major concentration on communication of useful information to health professionals, patients and health care providers
- The response to information, education and regulation should be monitored using objective criteria to determine the impact on health care practices
- Given the large impact of drug-related injury on health care economics (apart from humanitarian considerations), a broader view of drug safety should be taken, concentrating more on comparative benefit and risk of therapies and ways of reducing risk by good patient safety practices.
  - This means a greater concentration on education and communication
- Regulatory decisions over drug safety matters should be open to peer review, and, most importantly, include knowledgeable patients in the decisions
  - Panels of such patients should be available for consultations
- Legislation covering pharmacovigilance mostly concentrates on the collection of data. Requirements to demonstrate adequate procedures to respond to pharmacovigilance signals, and to perform impact assessments are more useful and should be in place for both regulators and industry
  - This includes timely performance of pharmcoepidemiological studies, and timely decision-making procedures that should lead to such studies.

## ***General***

This response is prompted by the report (Fraunhofer Institute Report – FIR), but does not attempt to analyse the report detail-by-detail. Therefore some of the points are already in the FIR, others are not. The FIR is timely because of the global discussion following the withdrawal of Vioxx by Merck. It is not the event itself, but that the discussion illustrates many of the strengths and weaknesses in pharmacovigilance[1].

A strong contention throughout this response is that considering drug safety as a primarily regulatory and epidemiological task is too limited, and that the gaze of pharmacovigilance must be predominantly focussed on the likely needs of individual patients and their health professionals. I emphasise that this is not only a serious philosophical point, but also there is major movement leading towards 'individualised health care' and genomics which will strongly influence the way in which we view drug therapies in the future.

Another contention is that the globalisation of the pharmaceutical industry, and the economic pressure both on it and health care regulators, leads to the rapid exposure of very different populations to new drugs, and old drugs used in new clinical settings. No one in drug safety can afford to ignore the global implications. These issues in turn have very wide implications on:

- how to consider individual case reports
  - particularly their analysis
- general decision-making

- how and where to do pharmacoepidemiological studies and their generalisability
- duplication of effort
- communication strategies
  - to other regulators and industry, as well as other broad stakeholders
  - to patients and health professionals

### ***The current situation***

There is a concentration on regulation and standardisation in the western world, particularly related to ICH, and therefore reflected in the EU. This has been valuable in bringing industry and regulators to many points of commonality, such as:

- standardised reporting forms for ADRs
  - what should be reported
  - a standardised transmission format, timelines and authorities
- periodic safety update reports
- risk management guidelines.

Because such aspects *are* feasible to standardise, there has been much concentration on the implementation and audit of the above activities. Such activities occupy time for both regulators and industry.

The assessment, analysis, and advice on drug safety issues is done by the Pharmacovigilance Working Party of all member EU states, coordinated by the EMEA. This has worked very well, both in apportionment of work amongst the EU states, and for exchange of views and expertise.

Final decisions are taken by the Committee for Medicinal Products for Human Use (CHMP) for EU registered products. Nationally registered products are still controlled by national decisions.

Very many sound results have come from this arrangement, which gives both a generally applicable form to major decisions and flexibility for country differences.

The EMEA has also developed the Eudravigilance system for the storage and transmission of ADR reports between it and member states. This duplicates much of what WHO already does, but there is provision for the WHO database at the UMC in Uppsala to receive the reports, from EMEA and vice versa. The WHO database also receives *all* suspected ADR reports from national centres, not only those that are 'unlabelled' and serious. It is noteworthy that older drugs are amongst the top ten reported drugs to the WHO database: a finding that has critical implications for patient safety in relationship to drug therapy. Other support developments such as Europharm for the storage of medicinal product information are being developed, and MedDRA is used for regulatory and clinical event terms.

### ***What should be developed in the future***

#### **The goals of pharmacovigilance**

The FIR is lengthy, and does not clearly spell out the essential goals of pharmacovigilance. In my view the essentials are:

1. To provide a) patients and b) their health professionals and c) health care providers (e.g. medical insurance companies) with the information they need to ensure the best therapeutic outcomes. To achieve this they need:
  - 1.1. Timely and understandable information on safety issues regarding specific drug therapy, which should include information about the potential for medical errors

- 1.2. Comparative effectiveness to risk information on reasonable alternatives for a given therapeutic indication
- 1.3. Adequate background information and education to be able to evaluate the information they receive
- 1.4. The time and resources to use the information in a meaningful dialogue in the clinical situation
- 1.5. Helpful clinical information to be able to diagnose an adverse drug reaction as compared with background disease, and other drugs' adverse reactions.
2. To be able to move from the first tentative signal of a problem to advice or other regulatory action
  - 2.1. Decisions which are well motivated and transparent at each step of the process are essential. There is little doubt that much of the public controversy about the regulation of medicines, and particularly the management of safety issues is the ongoing lack of transparency and therefore lack of understanding of the issues involved. The inclusion of public, and particularly relevant patient groups in monitoring the processes would largely help to avoid this problem.
3. The items mentioned in 1. and 2. should be considered from the time a medicinal product is first registered. The signal of a potential risk may arise from pre-marketing information and also gaps in knowledge which cannot be reasonably ascertained at the time of launch of a product. This is pro-active risk management. Class labelling is a particularly challenging aspect of pro-active risk management, but should not be automatically discounted.
4. It is essential to monitor the impact of communications and other regulatory action on the clinical practice of health professionals and on public health, and to optimise the effect on both from a health and economic perspective.

## ***Comments on specific issues***

### **Data sources and safety issue detection**

#### **Spontaneous reports**

Spontaneous reports are transmitted between parties (EMA, Industry, National Centres, WHO) according to a defined format. The process is audited for timeliness, but all aspects of the data management need quality assurance[2]. The coding of free text in a report is especially important (e.g. the miscoding of the SSRI 'lightning strike' reaction as 'dysaesthesia', since this was the nearest known term). This needs an international standard set of definitions and guidance. This process was started by CIOMS[3-5], but is neither widely used, nor is it complete.

- **The WHO/UMC would like to further this essential work collaboratively with the EU**

The WHO/UMC uses important internationally accepted tools to support its work in pharmacovigilance and would like to collaborate fully with the EU in making the best use of them. Medical terms are under constant development. The UMC is part of the WHO Family of International Classifications (WHO-FIC) Network. The FIC comprises the International Classification of Diseases (ICD), the Adverse Reaction Terminology (WHO-ART), the Anatomic - Therapeutic - Chemical Classification for medicinal products (ATC), the WHO Drug Dictionary, the INN, and others, related to other areas of medical and health care. All these classifications will be linked under the FIC process to make it easy to cross reference medical events with their causes.

There are preliminary discussions about the inclusion of SNOMED as a WHO classification as well as a recent proposal to map WHO-ART to MedDRA.

Improved interoperability between systems will aid health care processes greatly, related to medicinal product regulation, and beyond.

- **The UMC wishes to discuss and understand the EU's future requirements in medical terminologies. It wishes to correctly represent those needs in its work in the technical support of the WHO FIC Network. As a major business partner in the FIC Network, the UMC also wishes to find the best relationship with the EU to optimally develop the WHO global set of classifications.**

The UMC has a database linking medicinal products with their ingredients, with each product classified according to the WHO ATC classification. The data goes back to 1968, is updated continuously, and with fully controlled versions issued quarterly: the WHO Drug Dictionary.

A collaboration with IMS Health ensures the global coverage of data, which also includes many herbal products. Currently the database holds over 1,000,000 product records (including form – strength combinations) including 158,000 trade names and 55,000 unique combinations of ingredients (pharmaceutical products). There are 16,000 unique ingredient terms (and an additional 9,000 synonyms).

Herbal products are notoriously difficult to classify, and the WHO/UMC has worked with a variety of partners, including the Royal Botanic Gardens, Kew, UK, to produce a classification which is both internationally acceptable botanically (includes accepted Latin binomial name and authority name), and medically, as well as being useable in a database format to cover missing data and tracking partial synonyms[6-11].

- **The UMC would like to discuss if offering the ingredients data with unique identifiers to the ICH free of charge, including any ongoing maintenance, would further the EU's work, both within Europe and in ICH. It would also be helpful to know if the EU would require additional services, e.g. continuous access to new ingredients and provisional codes.**
- **The UMC would also like to discuss the possibility of the provision of other data relating to medicinal products which is under discussion in the ICH process, or any other data. As a preamble to such discussions the UMC makes it clear that the totality of its work is dependent on its self-funding capability, mostly from the medicinal product database. The UMC would therefore want to enter any discussions understanding that the essential work the UMC performs worldwide can continue and develop. In this respect a broader discussion of possibilities might be fruitful.**
- **The UMC would like to discuss the classification of herbal products, and its future development**
  - **This would include discussion on the important problems of herbal pharmacovigilance.**

Duplication of ADR report data is likely, given the potential for being sent the same data twice which is inherent in transmission to multiple recipients. There is an international decision for the WHO to maintain the global repository for international case reports. There are frequent calls to maintain and improve such an approach, and resources should be put into this internationally, and efforts should be made to ensure that data in the Eudravigilance and EU national databases are totally and accurately reflected in the WHO Database with adequate ascertainment and management of duplicates.

- **The WHO has an advanced, automated duplication detection system [12] and combined efforts on quality assurance should prove very useful.**

Under-reporting has been repeatedly mentioned as a fault in spontaneous reporting. Education of health professionals and the public over this is sorely needed. There is also an unfortunate concentration on the reporting of new, unexpected adverse reactions and new drugs. In order to fulfil the role of reducing iatrogenic disease, *all the concerns* of patients and health professionals regarding medicinal products and their adverse effects and adverse outcomes should be reported. There is abundant evidence that adverse drug event issues that are 'known' cause problems: obvious examples are interactions and off label use; more subtle are adverse reactions to generics due to excipients, and dosage issues in susceptible groups such as the young, the elderly and those with drug excretory problems.

Under-reporting could be reduced by the introduction of prompts into all software supporting patient record-keeping and prescribing and dispensing.

Pharmacoepidemiology has little role to play in signal detection, but a huge role in signal analysis. This is because:

- Large numbers of exposed patients are often needed, even for observational studies
- Hypotheses need to be clearly and specifically stated prior to the study

Signals may sometimes arise out of existing epidemiological studies. Also collection of prospective cohorts of all patients taking a new drug, with a hypothesis(es) based upon pre-marketing knowledge, or from spontaneous reports, in the style of prescription event monitoring (PEM), provide useful reassurance over quantification of adverse events. Novel ways of finding controls for such cohorts should be sought.

Signals may arise from many data sources, most of them computerised. A common problem to all of them is data extraction. Case report databases are large and there is a need for an efficient, automated tool to aid human search and analysis of such sets. Data mining approaches were initiated by the UMC [13-22] and triage strategies[23, 24] have been used as a routine for several years by the WHO/UMC. These have been tested in a prospective-retrospective study[25], and are adaptable for purpose. These kinds of strategies will be essential to signal detection in Eudravigilance in the future. The WHO/UMC has also used data mining on poison control, patient safety and patient record data sets, all with a positive effect on new knowledge finding. Complex pattern recognition of relationships between data fields has produced interesting results[13, 21, 26].

There is a view that large multi-purpose patient care databases may be used for signal detection, but there will still be questions of data quality and the tools used to find the signals. For example, data mining has been used by the WHO Collaborating Centre for Drug Monitoring on the IMS Health Disease Analyser database[1], and produced interesting signals, but each of them requires further elaboration as do signals from spontaneously reported concerns from health professionals and others. One advantage of the use of health care databases is that the signals might be better quantified

- **Ways of finding events related to drugs in computerised patient medical records have already been piloted by WHO/UMC .The WHO/UMC would like to co-operate better with the European institutions working jointly over the data management and analysis area**

The WHO /UMC has worked with the UK National Patient Safety Agency (NPSA). From this work and from many other pieces of intelligence, it is clear that patient reporting of adverse experiences is essential. Studies have been performed, but they are few. The overall view is that they contribute only a small amount of 'new' information, that is, new unlabelled adverse reaction reports[27]. There are other considerations however:

- Patient reports tell of what are their concerns. The 'quantitative' element is important, giving emphasis to the magnitude of a particular drug safety perception by the public. The response to such situations is not regulatory, but rather an information need for health professionals and/or patients
- Errors of miscoding (the SSRI 'lightening strike' reaction as 'dysaesthesia', mentioned above) and also under-estimations of severity can be detected by more attention to patient reports
- There are many examples of health professionals filtering out reports they do not believe in (events after insertion of IUCDs [28]; paraparesis following meningitis vaccination [29])

The WHO/UMC has recommended acceptance of patient/drug safety consumer reports [30]

## The legal framework and new legal tools

The current approach to legislation and to regulation is to try to control detail, particularly compliance by industry. This level of precision is often sought by both sides to clarify roles and responsibilities in a world where litigation by patients who have experienced adverse reactions is increasing. Whilst some of this is justifiable and necessary, there is a frequent complaint that concentrating on the detailed legal requirements for pharmacovigilance practice results in less time for product safety analysis.

Another aspect is whether patient safety is actually improved by the current legal framework. The legislation concentrates on performance in collection and transmission of information. It might be better to legislate on both industry and regulators to have in place ways of assessing impact of their activities on public health, and to show that these are active.

- For example, instead of legislation on the time transmit of ADR reports, there could be agreed quality assurance around the whole process from receipt of a report to action taken, and to impact analysis. It is the framework and transparency of the whole process which might be better enforced by legislation, not the detail.
  - (I would be most interested to know whether the ‘15 day reporting’ rule has ever been justified by any evidence as to its practicality: whether another, more relaxed time period would result in better, more complete reports. The current situation is a challenge in tracking follow-up information on cases and the potential for duplicate reports)

The results of industries’ analysis of safety information on their products is made available to regulators by Periodic Safety Update Reports. Such reports are very valuable but are very time-consuming both to prepare and to evaluate in their entirety. When the original CIOMS group developed the principle of PSURs, the idea was to keep the review work to a minimum. A main idea was that the company’s summary would have a strong legal implication: that this was the company’s view of the safety of its product, and could be seen as a part of its legal duty to warn. The remainder of the information was to act as a reference support for that opinion. It was not then envisaged that the volumes of information provided would need to be reviewed in the absence of an identifiable problem. The expectation that regulators will go through all the information currently included in a PSUR, and check the detail, is unreasonable and constitutes an in-principle form of over-warning, that is putting the onus on the reader to discern the ‘wood’ and the ‘trees’, when a clear message could be expected from the sender.

In my view the legal framework for pharmacovigilance should be reconsidered with a view to shifting the work that regulators and industry do to more productive areas for safety. Industry always faces the legal consequences of negligence, and particularly failure to warn. Therefore it seems logical that the PSUR summary findings should be represented in product information changes accurately. The regulator’s responsibility could be limited to making sure that happens and that PSURs are produced as agreed. This will be essential with more frequent PSUR submissions

There is another paradox related to over-warning and that is the multiplicity of the adverse event information that is still presented to health professionals and patients, often in a format that is difficult to read and understand.

- There needs to be new consideration of the product information as a legal document versus a helpful communication.
- Also product information is usually produced after a dialogue between regulators and industry. This relationship should cease and regulators should be the brokers who ensure that the product information is acceptable to relevant patient groups, rather than trying to act on their behalf.

## Decision-making in pharmacovigilance

The key decision-making steps are:

1. What signals to evaluate further based on the potential seriousness, frequency of reported concerns and diagnostic difficulty (e.g. where there is the potential for confounding, which may also be considered a risk factor)
2. What specific studies would be most helpful in taking the selected signals further, which might include mechanistic studies, epidemiological studies, intensified monitoring and in depth investigation of case reports. The timescale for completion of additional work should be determined and enforced.
3. How to communicate with health professionals and/or the public over potentially serious but incompletely investigated signals including what actions are being taken
4. To determine the impact of new information of the target medicinal product on the relative effectiveness and risk of therapies (including non-drug therapies) for a particular clinical indication, and which may be relevant for identified at-risk groups. At-risk groups should include those that may be at risk through predictable off-label use such as in paediatrics and any possible misuse potential/overdose risk
5. How to communicate with health professionals and/or the public the results of the analysis in 2.

A major goal should be to have true transparency surrounding these decisions (see above and below). The need for care in managing a signal in order not to cause confusion and a 'drug scare' is recognised, but the public is not served by silence over evolving safety issues either. This dilemma has been debated (see Erice report[31, 32] ), and CIOMS [33-35] workshops on have outlined factors that need to be considered when considering and reporting on drug safety. Of the several, four may be key:

- Information quality
- Context: seriousness of treated disease, comparison with other treatment options from a benefit risk perspective
- A sensitivity analysis: best-case-worst-case.
- Follow-up.

The decisions of most regulatory agencies do not give this information relating to the decision-making processes when publishing signal information. The steps 1-5 above are usually followed in some way, but there is no peer review of the process, and the end result is not communicated in the context of the four bullet points.

Two critical issues arise over decisions about drug safety, both typified by the Vioxx situation.[1]. The first is covered in the FIR and relates to the time which elapses from the first signal to a 'definitive' decision. In my view it is not that the process is unduly slow, but that the complexities of getting firm answers in safety are many. These are not understood generally, and there is a major educational challenge. On the other hand there is a logical public argument about failure to provide information when there *may* be a cause for concern. A second issue is that decisions about one drug affect the use of other competing drugs, and there is far too little information about a range of reasonable courses of action for health professional. It is always said that providing recommendations about preferred therapy interferes with their professionalism, but the regulatory action taken does that anyway.

- **The UMC would like to work with the EU to develop standard operating procedure/guidelines that can support the decision-making processes, and indeed the data collection triage and analyses that must support the decisions. These would be based on the Erice and CIOMS work.**

## Impact of communications and actions

- This is the absolute priority for the future.

Currently, the regulator's work is often deemed to stop when information has been sent out or action taken. When there is more doubt about an adverse reaction, the action is a labelling change. In order for practitioners to know about such a change, they would have to read the product information constantly: the public would have to perform a historical check for changes: even if they were knowledgeable enough to consider the issue, they would probably lack any prior experience.

The drug safety world is one where it seems to satisfy the experts that they know about a problem and provided information. This is even so with serious and fairly certain ADRs when a single, 'Dear Health Professional' circular is all that is deemed necessary to manage the situation.

Communication is a two-way process, with the feedback loop of checking understanding and appropriate action. This does *not* mean that practitioners should always follow directives, rather that they should understand the information given and incorporate this into their daily practice.. It is the giver of information that should check on the response.

Communication is always given and received in a particular context. The recipient of information may be health professional (of various kinds), or patient, health care provider, lawyer, or general public. They will be of various educational backgrounds, and so on. The message must be given in ways that consider different contexts. The message may take different forms, and the appropriate action in response to the message may also differ.

Communication is a professional art and science: drug safety matters are complex[36, 37] . Considering, however, the cost and effort involved in developing a drug, and performing pharmacovigilance, the amount spent on actually assessing whether the drug is used optimally, or whether pharmacovigilance does anything at all for public health is trivial. Patient safety in relationship to drugs is more influenced by problems with drugs whose safety profile is well known, than the rare reactions to new drugs which is the main thrust for today's pharmacovigilance [27]. The WHO/UMC has been working for some years on the provision of information, and entering into a dialogue with some national centres over the issue of communication and impact analysis [31, 32, 38]

Developing countries often complain that they are caught unawares when a major developed country decision on drug safety is published in the press before they know about it. Many countries, including EMEA are very good at informing the WHO/UMC about decisions they have made, but this does not solve the problem because the notice time is too short for regulators to react responsibly. Situations also arise when decisions in one regulatory body or another around the world apparently conflict. Both kinds of situations could be avoided by better communications and prior warning of topics under discussion.

- **The WHO/UMC operates a confidential e-mail distribution list for discussion about drug safety issues (Vigimed). We would propose that this be used more actively by the developed country regulators to avoid this problem. This will require some consideration of legal matters which constrain some countries, and the EMEA**
- **There are existing networks between some regulatory authorities: USA, Canada, Australia, Sweden and others. These networks could be expanded, and perhaps there is a place for co-operating regional networks, reflecting different public health needs.**

Education is a special and important form of communication. The UMC has offered worldwide courses in pharmacovigilance for professionals at all stages of their work in the field, including non-health care players. It has also produced information for the public on the context and issues of drug safety[39]. This is acknowledged in the FIR.

- **WHO/UMC would like to fully co-operate in any development in the communication and education area, and offers its consult team to aid this work.**
- **WHO/UMC would like to co-operate in coordinated efforts to gain information on the impact of pharmacovigilance activity on patient safety. A small international pilot project is being planned within the framework of the WHO Programme for International Drug Monitoring.**

## **Monitoring compliance and quality management**

Compliance has been mentioned in the legal section above. Many studies of compliance have shown that it is mainly improved by the demonstration of the value of the system to the subject. Studies on doctor reporting of ADRs have shown that reduced workload and useful feed back increase compliance[40].

Quality management of data is essential [2, 41]. Various international standards organisations exist, the WHO having taken the lead over many health care standards, particularly over terminologies/ thesauri/ dictionaries/ classifications and definitions. Working within the WHO Family of International Classifications, and other international standards organisations such as ISO and CEN, the UMC has knowledge in this general area. It routinely develops tools and quality assurance methods for data input, storage, collation and analysis. The UMC offers all this knowledge, data and analysis to all participating countries of the WHO Programme for International Drug Monitoring. In this respect the EMEA has always been regarded as a ‘national centre’, and has had access to the same material and services available to individual countries within the EU.

- **The WHO/UMC seeks to understand how it may co-operate better with the European institutions to help in the pharmacovigilance work of the EU, and jointly how the EC and the UMC may foster global harmonization and development in the safety of medicinal products.**

## **Other comments**

In its global work in pharmacovigilance, the WHO/UMC is constantly reminded of the impact of decisions (as above), and general activities made in one country have on others. This is particularly true of the ‘developed’ world on the ‘developing’. The EU is the only other international pharmacovigilance group than WHO, though WHO’s role in international medical affairs is largely advisory, differing from the EU which can make binding decisions on member states.

All EU member countries except Slovenia are also WHO members, and the need to both obtain the benefits and fulfil the duties of membership should be as easy as possible: differences will occur between countries according to their special requirements but should be minimised and justified when there is need.

Co-operation and partnership at all levels would seem not only desirable, but essential to avoid duplication of efforts and lack of harmony.

General developments which the EU (and other developed countries) makes are often impossible for resource poor countries, even when the developments of themselves are very desirable. The WHO/UMC constantly struggles with this challenge in pharmacovigilance, since it seems that countries with limited resources are destined to have not only the heavier burden of disease, limited health care resource in general, limited supplies of medicines (some more toxic older medicines as well as higher levels of counterfeit and poor quality drugs), but also suffer from not being able to develop regulatory and drug safety systems in an optimal way. This includes technology transfer issues such as the implementation of MedDRA and other ICH initiatives, CIOMS recommendations and so on.

- As one of the major global policy developers and economic powers, EU support for the delivery of needed and requested tools for drug safety to member states of the WHO International Programme on Drug Monitoring would be welcome

## Disclaimer and acknowledgement

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