

*REPORT OF THE AD HOC WORKING GROUP
PROGRESS ON IMPLEMENTATION OF
THE EUROPEAN RISK
MANAGEMENT STRATEGY*

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HEADS OF MEDICINES AGENCIES (HUMAN)

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I Introduction

This Report provides an overview of progress in implementation of the European Risk Management Strategy (ERMS).

Delivery against the original priorities for action is assessed, in terms of a revised mandate for the PhVWP, a completed survey of resource, work sharing arrangements in place and strengthened capability to deliver Community wide action on pharmacovigilance. Examples are highlighted where the impact of the ERMS on the capability of the Community system to protect and promote public health has been demonstrated. These include identifying important lessons to be learnt following the withdrawal worldwide of Vioxx (rofecoxib); the success of co-ordinated communication on a drug safety issues, such as on Hormone Replacement Therapy; and the effective delivery of co-ordinated action in response to a safety concern spanning the licensing routes of the European system - antipsychotics and stroke.

II Background

The Heads of Medicines Agencies (Human) Ad Hoc Working Group on ERMS was established up in July 2002 in the aftermath of the cerivastatin withdrawal to consider the action needed to strengthen pharmacovigilance systems so that all medicines, whether centrally or nationally authorised, could benefit from the same high standards of safety monitoring. The agreed mandate for ERMS comprised 5 objectives in order to;

- Build on National Competent Authorities (NCAs) resources and expertise and incorporate the EMEA's role in the co-ordination of the supervision of products authorised in the Community;
- Support consistent robust decision making;
- Ensure accessible information on safety, including information exchange between NCAs;
- Reduce duplication of work;
- Be demonstrably effective in protecting public health.

III Progress

The initial report of the Ad Hoc Working Group on the establishment of the Strategy was published in January 2003 and can be found at <http://heads.medagencies.org/> (1)

Initial priorities for action

The Heads of Medicines Agencies agreed 5 key priorities for initial action:

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- Review of the mandate of the Pharmacovigilance Working Party (PhVWP);
- High level survey of EU pharmacovigilance resources;
- Secure best use of scarce resources for pharmacovigilance;
- Proposals to strengthen pharmacovigilance communications and information exchange;
- Guidance on Risk Management Plans.

Each of these are considered below as to what has been achieved.

Review of the mandate of the Pharmacovigilance Working Party

Robust decision making is central to the proposed “model” for achieving excellence in pharmacovigilance(2). The Pharmacovigilance Working Party (PhVWP) was established to provide a forum for discussion and to make recommendations on all matters relating directly or indirectly to pharmacovigilance. The PhVWP has a dual reporting line, i.e. to the CHMP and to National Competent Authorities (NCAs).

For medicinal products authorised through the centralised procedure and for medicines which have been referred to the CHMP in accordance with Community procedures, these recommendations are given to the CHMP. Upon request of NCAs, the PhVWP provides recommendations for non-centrally authorised products to the Heads of Medicines Agencies and to the Mutual Recognition Facilitation Group (MRFG). The mission of the PhVWP is to provide advice on the safety of medicinal products authorised in the European Union and the investigation of adverse drug reactions, to enable effective identification, assessment and management of risk, at any phase in the product life cycle.

Since its start in 1995, the PhVWP has become the appropriate forum for the exchange of information between its members, for reaching consensus on safety issues facing the Community and the development of procedures and guidelines.

In the face of new and evolving challenges, the Ad Hoc Working Group, in collaboration with the CHMP, developed a revised mandate for the PhVWP, setting out the following key responsibilities:

- Evaluation of potential drug safety signals arising from spontaneous reporting, including those identified from the EudraVigilance database, and other sources;
- Provision of advice on confirmation and quantification of risk and on regulatory options;
- Advising on Risk Management Plans and programmes;
- Setting standards for procedures and methodologies to promote good vigilance practice;
- Promotion of communication and exchange of information between EMEA and NCAs;
- International co-operation.

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This revised mandate enables the PhVWP to provide enhanced support to the CHMP and NCAs and is an important tool for the successful execution of the European Risk Management Strategy.

An important consideration is how far this revised mandate has been implemented in practice in relation to the PhVWP, the CHMP and the Member States. Further consideration will need to be given to whether changes are necessary to optimise the role of the PhVWP in the decision making process.

High level surveys of EU Pharmacovigilance resources

The purpose of conducting the high level surveys was to gain an overview, informed by data, of the overall resources of the EU network. A first high-level questionnaire survey in 2002 gave a snapshot of pharmacovigilance resources in the 15 Member States who made up the Community at that time. A second follow up survey of the same 15 Member States was undertaken in 2004 and later in the same year, a consolidated questionnaire was sent to the 10 Member States who joined the EU earlier in the year.

The first survey showed limited staff resources (around 300 full time equivalents), the majority of whose time was spent on national products, with an equal split on data entry and risk assessment. It showed a heavy reliance on spontaneous adverse drug reaction (ADR) reports, the majority on paper, with Periodic Safety Update Reports (PSURs) a significant workload (over 17,000 in total). Thirdly, the survey showed that all NCAs had dedicated resource for disseminating drug safety information to health care professionals and the public.

The second survey in 2004 enabled more detailed exploration of the issues raised by the first, and focussed at Sweden's suggestion on the range of evidence available to NCAs for detection and assessment of drug safety signals. A workshop held in June 2004 jointly by the ERMS Ad Hoc Working Group and PhVWP brought together the new and original Member States to consider the findings of the surveys and discuss the way forward.

The Third survey to new Member States showed there are limited staff resources (approximately 36 full time equivalents in the 10 MSs) with some reliance on external experts. The major data source is paper based spontaneous ADR reports with a total number received across the 10 MSs in 2004, of around 2800 reports. The cumulative number of reports held of databases was approximately 47,000 with 43,000 being held by one MS. This contrasts with the total number of reports in the earlier survey of 15 Member States of over 1 Million. Minimal signal generation is carried out due to the small number of reports. The majority of MSs are active in trying to develop electronic reporting but most are reliant on resource external to the pharmacovigilance unit. The majority have some support in dissemination of drug safety information.

Better use of existing resources for pharmacovigilance

The results of the questionnaire survey underline first and foremost the limited nature of resources dedicated to pharmacovigilance in the EU network. Avoiding duplication of effort is therefore a priority. Under Netherlands' and UK leadership, a work sharing process has been developed to mitigate the level of duplication of effort on PSURs. A

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pilot study commenced in January 2004 with volunteers from 5 NCAs (Denmark, Germany, Netherlands, Sweden and UK) and a set of principles agreed by MRFG/PhVWP is now in place. The principles were adopted by the HMA-human in November 2004, following legal advice from the European Commission (3).

An ad hoc working group on the synchronisation of PSUR submissions has been established. Representatives from PhVWP, MRFG and the industry associations participate in the group. Challenges remain in order to make best use of this initiative and to effectively free up Member State resource but experience gained from the pilot PSUR assessment work sharing project can be used to refine the principles. There also needs to be consideration of success criteria for the pilot in terms of resources saved and safety updates delivered etc.

In view of the importance of further building on the work sharing principle, more work needs to be done on the other areas of pharmacovigilance for which work sharing could be developed using the "reference or lead Member State" principle e.g. development of risk management plans, materials for communications etc. The question of a legal base for such arrangements also needs to be further explored. If appropriate, the Commission could consider proposing changes to EU law as soon as possible after implementation of the changes later in 2005.

EudraVigilance

EudraVigilance is the EU data processing network and management system which contains suspected adverse reaction reports to medicines licensed across the EU. Such reports are received electronically from the EU Regulatory Authorities and the pharmaceutical companies. The system, which has been developed according to internationally agreed standards, was launched in 2001. EudraVigilance will be an important pillar of the European Risk Management Strategy with a view to facilitating the conduct of pharmacovigilance at EU level, as a tool for data collection and analysis and will provide automated tools for signal detection.

Since its launch in December 2001 major efforts have been undertaken to implement EudraVigilance at the level of all EU Regulatory Authorities and some 3500 pharmaceutical companies. In addition, the consequences of an enlarged EU had to be taken into account, as well as the implementation of new Community legislation on clinical trials. As a result, it is now possible to report electronically SUSARs (Suspected Unexpected Serious Adverse Reactions) stemming from clinical trials as well as ICSRs (Individual Case Safety Reports) in the context of post-authorisation pharmacovigilance data.

Major initiatives in 2004 relate first to a further development of the EudraVigilance database and data processing network. These initiatives mainly relate to new functionalities such as the development of a special web-based tool designed to support the electronic reporting by small and medium-sized enterprises and non-commercial sponsors of clinical trials conducted in the EU, and the implementation of a first pilot version of automated tools for signal detection.

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Taking into account the fact that the implementation of EudraVigilance by the pharmaceutical industry and the Member States did no progress as expected, initiatives have been taken to facilitate the electronic reporting of ICSRs. A large scale-training programme for NCAs and the pharmaceutical industry was developed by the EMEA and launched in May 2004. Furthermore, actions were undertaken to speed up the population of EudraVigilance by organising individual implementation meetings with each of the NCAs and by reviewing, through an ad-hoc expert working group, policy, compliance and regulatory aspects stemming from the first experience gained with electronic reporting by NCAs and the pharmaceutical industry.

Arrangements for sharing regulatory information

The global nature of drug safety monitoring requires effective information sharing mechanisms, which put public health first. On 12 September 2003 Confidentiality Arrangements were concluded between the European Commission, the EMEA and the FDA in the context of regulatory co-operation and transparency between the US Government and the European Commission. The Confidentiality Arrangements allow the EMEA, the FDA and the European Commission to exchange information as part of their regulatory processes, both pre-and post-authorisation. The withdrawal of Vioxx suggested a need to revisit the issue of confidentiality agreements with the US FDA encompassing nationally authorised products (including mutual recognition ones).

The types of information covered include regulatory issues, scientific advice, orphan drug designation, inspection reports, marketing approvals and post-authorisation surveillance information. The sharing of product-related information is limited to medicinal products evaluated or authorised in accordance with the EU Centralised Procedure, as well as medicinal products authorised at national level by the EU Member States, subject to arbitration or referral in accordance with Community procedures.

The primary aim of the Confidentiality Arrangements is to strengthen communication between the regulatory authorities and reinforce public health promotion and protection. The implementation will take place in a step-wise approach, whereby the first phase will concentrate on the establishment of an educational programme, the establishment of procedures for the exchange of documents and information and the subsequent exchange of documents and information, and the possibility for staff to be exchanged between or seconded to respective organisations. In a second phase an audit will be undertaken to evaluate whether exchanges were timely, relevant, and mutually beneficial for the effort expended, and include recommendations for changes to the scope of interaction, in accordance with the terms of the Confidentiality Arrangements.

IV Examples of impact of ERMS on public health

During the course of the work of the Ad Hoc Working Group there have been notable examples where the impact of the ERMS on the capability of the Community system to

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protect and promote public health has been demonstrated. And the Group has been alert to the need to ensure any lessons from these case studies are identified and learned.

Vioxx

The public awareness of the effectiveness of drug safety monitoring was bought in to sharp focus when on 30 September 2004, Merck, Sharp and Dohme announced its withdrawal of Vioxx (rofecoxib) world-wide. The company's decision to withdraw the product was based on new clinical trial data. The safety concern could not have been identified through spontaneous reporting. The Ad Hoc Group nevertheless identified important lessons to be learnt and actions which should be taken forward.

The withdrawal of Vioxx raised legal issues for both the Commission and Member States. Member States needed to be clear on the obligations in national law to require MA holders to notify/agree communications on safety issues. The question of the impact of stock-market rules on pharmacovigilance obligations was relevant to both national and EU legislation. HMA (Human) have highlighted the need for the Commission to consider proposing to strengthen the legislation after the coming into force of the new provisions in November 2005. Such changes could be achieved through the Standing Committee procedure.

Additionally, there is support for a code of conduct, agreed with industry, to set out the principles/ethical issues which should be followed in such circumstances. This work might also provide for wider awareness, including by academia/journals on the need for co-ordinated communications on drug safety issues with potential public health impact.

Hormone Replacement Therapy (HRT)

An example of successful co-ordination of communication on a drug safety issue was that of HRT. In this case, the role of the PhVWP (and HMA Human itself) in co-ordinating national communications, both in terms of timing and of the key public health messages, was crucial in ensuring balanced, effective communications in all concerned Member States.

An ad hoc expert group, under the auspices of the CHMP, was demonstrated to be an important model for using expertise and reaching consensus without the need for CHMP referral. The MRFG expert sub-group for the HRT core SPC has shown such a model to be successful in practice. This MRFG sub-group used the expertise of PhVWP to agree a core SPC for HRT products that will form the basis for future MR procedures. When new data became available, the group was quickly reconvened and an updated position reached. Member States are able to use the agreed European scientific and regulatory position as a basis for national implementation thus assisting both horizontal and vertical harmonisation across Member States.

Antipsychotics and stroke

In the case of antipsychotics and stroke, the different routes of authorisation of the products and the need for clear and the need consistent communications across Europe was a challenge. When it became clear that there was evidence of an increased risk of stroke associated with risperidone (national) in older people with dementia, that olanzapine (centralised), appeared to be associated with a similar risk and that such a

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hazard could not be excluded for quetiapine (Mutual Recognition) the EMEA urgently convened a special group to consider the issues (NL, Fin, De, UK, EMEA). PhVWP had already asked for a communications package to be prepared and when CHMP reached a conclusion on olanzapine, co-ordinated communication at an EU and Member State level was achieved.

These examples serve to demonstrate the potential for effective public health action when the competent authorities work together to achieve co-ordinated approach.

V Forward look and next steps

Key issues in relation to the five priorities for action are suggested. These include:

In relation to the PhVWP, the reforms already put in place were based on sound principles but have yet to prove themselves in practice. Further strengthening of the operation of the Working Party and strengthened secretariat may be considered. Implementation of these changes and the delivery of the new mandate should be closely monitored by the EMEA Management Board and the HMA (Human).

The questionnaire survey of pharmacovigilance resources suggests that the capability of the network is largely focussed in a few well resourced Member States while in others the function is less well developed. Development of further work sharing mechanisms and building partnering arrangements may offer ways forward, as part of an overall strategy to strengthen the EU pharmacovigilance network.

More work needs to be done to achieve the potential benefits of work sharing, in particular, other areas of pharmacovigilance for which work sharing could be developed using the "reference or lead Member State" principle e.g. development of risk management plans, materials for communications etc.

The question of a legal base for such arrangements also needs to be further explored so that the Commission are in a position to propose making changes if appropriate as soon as possible after implementation of the changes to EU law later in 2005. Ensuring effective pharmacovigilance in the immediate post-launch phase needs particular consideration.

The Commission, EMEA/FDA confidentiality agreements have the potential to mark an important step forward but HMA/Member States will need to fully engage in this process if European citizens are to benefit fully from the potential gains to public health in sharing information. It will be important to be cognisant of the debate on the need to consider risk and benefit as a whole rather than separately.

HMA (Human) requested the Commission strengthen the legislation and the Commission has indicated it is willing in principle to consider amendments to the EU legislation after coming into force in November 2005. Such changes could be achieved through the Standing Committee procedure.

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But the withdrawal of Vioxx suggested a need to revisit the issue of confidentiality arrangements with the US FDA encompassing nationally authorised products (including mutual recognition ones).

The EudraVigilance database is intended to be an important pillar of the European Risk Management Strategy. Much progress has been made and further development is underway but important horizontal issues remain to be addressed if the promise of EudraVigilance is to be delivered.

VI Final thoughts

In all the areas identified as priorities in the European Medicines Regulatory System, all can be said to have responded to change and to be continuing to develop. The European Commission assessment of the Community system of pharmacovigilance⁽⁴⁾ offers the opportunity not only to draw these threads together but also to look forward to determine the critical success factors for the ongoing development of the Community system.

The work of the Heads of Medicines Agencies (Human) will also be crucial in developing how the Member States will respond to the challenges that lie ahead in developing a road map for the NCAs in which the public can have confidence. More strategic thinking on what additional measures need to be taken by the EU Regulatory System in order to contribute to the best evidence approach is necessary and to further enhance effective communications – at every level.

The challenge is delivery of a European system greater than the sum of the parts. It is clear that the central role of the EMEA has changed and developed over time and will continue to do so. And in the same way, the role of the NCAs and their defined roles and responsibilities are also changing in the light of the focus of considerable attention. A strengthened Community system will need to build on these respective roles. This will ensure the capacity of the European system is maximised by making best use of the strengths, including multiple sources of data to support decision making and the capacity for joint working, but with the flexibility to deliver outcomes capable of implementation in the enlarged Community.

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- 4 (<http://pharmacos.eudra.org/f2/pharmacos/new.htm>)