

## **Public Status Report on the Implementation of the European Risk Management Strategy (Reporting Period Mid 2005 – Mid 2007)**

### **I Introduction**

Heads of Medicines Agencies agreed during their 25 November 2005 meeting on how to further implement the European Risk Management Strategy (ERMS). This resulted in the document “Implementation of the Action Plan to Further Progress the European Risk Management Strategy: Rolling Two-Year Work Programme (Mid 2005 – Mid 2007)”, which provides information on the initiatives envisaged up to mid 2007.

As per the transparency arrangements in the aforementioned document, information on the follow-up to all the announced initiatives since mid 2005 up to the end of May 2007 is provided in the current Status Report. Such Status Report was agreed upon by Heads of Medicines Agencies during their July 2007 meeting under the Portuguese Presidency, and subsequently made public.

### **II Current Status of the ERMS Implementation**

Overall, very good progress has been achieved on the implementation of the ERMS, and this in various fields. A summary of the main achievements is provided below and more details can be found in Annex 1. Such main achievements have been classified into three areas, i.e. the implementation of the new legal tools stemming from the 2005 Community legislation, the undertaking of additional work to achieve a more intensive drug monitoring system and a strengthening of the operation of the EU Regulatory System networking model, and in particular its pharmacovigilance/safety of medicines monitoring component.

#### ***Implementing new Community legislation***

As part of the further implementation of the 2005 Community legislation package, activities during the reporting period focussed on the drafting of guidance on the new legal provisions, for both pharmaceutical industry and the Competent Authorities. Updated guidance in the field of pharmacovigilance/safety of medicines monitoring has been made available through a complete revision of Volume 9A of “The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use”. One of the most important initiatives concerned the field of risk management plans where the focus has been on the implementation of this novel concept and on the subsequent monitoring of such implementation through the Review and Learning project. This should result later this year in a structured dialogue between EU Regulatory Authorities and pharmaceutical industry on current experiences with EU risk management plans, identified opportunities for improvement and resulting remedial actions.

### ***Undertaking additional work to achieve a more intensive drug monitoring system***

Improvements in the area of spontaneous reporting of adverse drug reactions focussed on the further implementation of EudraVigilance and the introduction of additional functionalities. This resulted in an increasing number of National Competent Authorities (NCAs) and pharmaceutical industry reporting electronically, although it needs to be stated that 100% compliance still has not yet been achieved. In addition, a number of implementation issues could be observed, primarily in relation to the quality of the submitted data and the legal reporting deadlines. This led to remedial action which should result in further improvements both in the pre- and the post-authorisation phase. Important preparatory work was undertaken with respect to the validation of the EudraVigilance Datawarehouse and Analysis System (EVDAS). This should enable a roll-out of EVDAS to the NCAs during the 2<sup>nd</sup> half of 2007. Such roll-out as well as the availability later this year of guidance on the use of statistical signal detection methods in EVDAS should lead to an improved use of the EudraVigilance database in the overall conduct of pharmacovigilance at EU level.

Acknowledging that spontaneous reporting and its still rather novel feature of electronic transmission of data remains a cornerstone of the EU Pharmacovigilance System, various initiatives have been undertaken to complement knowledge obtained through the spontaneous reporting scheme by introducing the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) project, which should facilitate the conduct of multi-centre post-authorisation safety issues. Further to the identification of various centres across the EU, efforts now focus on the organisational and operational aspects of such network.

In addition, discussions with the European Commission on research aspects in the context of the Health Theme of the 7<sup>th</sup> Framework Programme, which are in line with the European Commission's "Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance" as announced in February 2007, have resulted in a first tangible result. Such result could be noted in the field of NSAIDs with concrete proposals made by the EMEA/CHMP to the European Commission as regards the various aspects to be covered in further research with respect to NSAIDs. This will be complemented later this year with the production of a list of the top five public health issues in drug safety to be further studied in the context of post-authorisation studies on the safety of medicines.

### ***Strengthening the operation of the EU Pharmacovigilance System***

Further improving the quality of the work performed by regulators was another domain where considerable progress could be noted during this reporting period. This concerned both the introduction of a formal peer review system at CHMP level for centrally processed applications, as well as activities to strengthen the methodology for benefit/risk analysis in order to improve the consistency of decision-making. Furthermore, the scientific expertise at PhVWP level was strengthened taking into account the outcome of a gap analysis of the available expertise.

Efforts on a further strengthening of the organisation and operation of the EU Pharmacovigilance System focussed on strengthening the interaction between the PhVWP and the CMD(h) and optimising the operation of the PhVWP. Preparatory steps were also taken for the development of an EU Regulatory System Incident Management Plan for medicines for human use (irrespective of the licensing route), which should become available towards the end of 2007. Furthermore, important progress has been made on optimising the utilisation of scarce resources at the level of the NCAs by implementing the work-sharing concept in the field of assessment of Periodic Safety Update Reports (PSURs).

Important work was also undertaken in the context of the pandemic influenza preparedness, not only in relation to the provision of guidance for pharmaceutical industry when submitting a marketing authorisation application for a pandemic influenza vaccine, but also in terms of the availability of a crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals.

## Details on the Progress Made on the ERMS Implementation During the Period Mid 2005 – Mid 2007

As stated in Chapter II “Current Status of the ERMS Implementation”, there has been good progress with the further implementation of the ERMS during the period mid 2005 – mid 2007. Details on the current status of implementation have been grouped per priority area, as described below.

### **I Priority Area: Implementation of new Community legislation**

- Guidance both for pharmaceutical industry and EU Regulatory Authorities (e.g. the CHMP) has been drafted in relation to several new legal tools to further strengthen the safety monitoring of medicinal products. This resulted in a revision of Volume 9A of “The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use”, which was subject of an external consultation exercise. One of the major initiatives concerned the drafting of guidance with regard to the new concept of risk management plans.
- Work also progressed in the field of a strengthening of transparency as regards the safety of medicines. Whilst some work could be finalised (such as the drafting of guidance on Direct Healthcare Professional Communications (DHPCs) which has been finalised after external consultation), other work is still in a preparatory phase, for instance in relation to the accessibility of the EudraVigilance database to the various stakeholders and the timely provision of targeted pharmacovigilance related information.

### **II Priority Area: Complementary initiatives to arrive at the envisaged intensive drug monitoring system**

#### *Area of risk detection*

- Important progress has been made with respect to the speeding-up of the implementation of electronic reporting to EudraVigilance in accordance with ICH standards, both at the level of the National Competent Authorities (NCAs) and pharmaceutical industry. By the end of April 2007, 28 NCAs and 249 Marketing Authorisation Holders (at headquarter level) are in production with the EudraVigilance Post-Authorisation Module, whereas 197 Sponsors are reporting to the EudraVigilance Clinical Trials Module.
- Due account has been taken of experiences gained with the electronic reporting to EudraVigilance. Following a survey performed at both the level of the NCAs and pharmaceutical industry, an Action Plan has been developed to address a.o. identified non-compliance with the quality of Individual Case Safety Reports (ICSRs) and the legal reporting deadlines. Such Action Plan was agreed upon by Heads of Medicines Agencies during their April 2007 meeting and by the EMEA Management Board during its June 2007 meeting, and an Implementation Plan is currently being developed by the EudraVigilance Expert Working Group.

- Further work was also undertaken as regards the introduction of additional functionalities for EudraVigilance. Following a successful internal and external User Acceptance Testing of the EudraVigilance Datawarehouse and Analysis System (EVDAS), a validation exercise is currently being carried out in view of the roll-out of EVDAS to the NCAs during the 2<sup>nd</sup> half of 2007. Furthermore, a guideline on the use of statistical signal detection methods in EVDAS was drafted and the comments obtained in the context of the external consultation exercise are currently being reviewed.
- Important input has been provided in relation to the Innovative Medicines Initiative in relation to the development of the Strategic Research Agenda in the field of pharmacovigilance. Discussions with the European Commission, involving both DG Enterprise and DG Research, have resulted in the inclusion of the topic “Relative safety of NSAIDs” in the 2007 Work Programme for the Health Theme of the 7<sup>th</sup> Framework Programme. Further to a knowledge “gap analysis” performed at CHMP/PhVWP level, information has been provided to the European Commission at the beginning of 2007 with respect to the need for additional data, the relevant issues to study, the proposed approaches and study designs, as well as the research output. Furthermore, the CHMP/PhVWP will draw-up a list of the top five public health issues in drug safety affecting groups/classes of medicines including off-patent products. This is in view of a possible inclusion of other topics under the 7<sup>th</sup> Framework Programme, under the umbrella “post-authorisation studies on the safety of medicines” for subsequent calls for proposals.
- In order to further strengthen the post-authorisation monitoring of medicinal products, the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) project was launched. By concentrating available expertise and research experience in the field of pharmacoepidemiology and pharmacovigilance across the EU, ENCePP provides the unique opportunity to facilitate the conduct of multi-centre “independent” post-authorisation safety studies. The project consists of several phases. The first phase, aiming at identifying the various centres across the EU has been finalised. This has resulted in the establishment of a general inventory of 55 centres and a paediatric inventory of 8 centres following a survey at the level of the Member States. In addition, a third inventory following feedback from pharmaceutical industry has been established, whilst a fourth inventory of pharmacoepidemiological databases and useful patient registries is envisaged. The project is now focussing on the development of a structure and model for the future network.

### *Area of risk assessment*

- Work has been undertaken to reinforce the scientific expertise at PhVWP level. After a gap analysis of the available scientific expertise the identified missing/insufficient expertise has been complemented through cooptation of PhVWP members in the fields of pharmacoepidemiology, risk management, risk communication, biotechnology/vaccines/emerging therapies, statistics and methodology, paediatrics and immunology. Discussions also started on a further optimisation of the operation of the PhVWP, primarily in relation to its interaction and output to the CHMP. Furthermore, the interaction between the PhVWP and the CMD(h) has been strengthened and formalised, building on the work already undertaken through the Best Practice Guide on the cooperation between the PhVWP and the former MRFG.
- The existing peer review systems for the scientific work undertaken at CHMP level have been reinforced through a more formal peer review by CHMP members concentrating on the timeframe up to the adoption of the List of Questions for centrally processed applications. Such peer review includes the aspect of risk management plans submitted by applicants.
- Activities to reinforce the methodology for benefit/risk analysis with the aim to improving the consistency of decision-making focussed on the development at CHMP

level of a report on benefit/risk assessment models and methods. A 2-step approach is being applied. The first step will concentrate on integrating the most useful features of the models into CHMP guidelines and assessment report templates. In a second step further research into the methodology of benefit/risk assessment will be undertaken. The CHMP report has undergone external consultation and comments received are currently being reviewed.

#### ***Area of risk minimisation***

- As already elaborated upon, the concept of risk management plans has been implemented as part of the new legislative provisions. A Review and Learning Project has been set-up whereby risk management plans both for centrally authorised products and non-centrally authorised products are being reviewed. The first phase of the project has been concluded and has revealed that the EU risk management plans have been of varying quality during the early period of submissions, but there has been a successive improvement of the compliance with the available guidance over time. Measures to address the identified weaknesses will be proposed in view of a discussion between regulators and pharmaceutical industry during a workshop to be organised either later this year or at the beginning of next year.

#### ***Area of risk communication***

- Work in this field primarily focussed on streamlining the provision of information to Healthcare Professionals by making available guidance on DHPCs. Principles for the content and format of DHPCs have been established in such guidance and situations where dissemination of DHPCs should be considered have been described. In addition, work has started to develop an EU Regulatory System Communication Strategy on emerging safety related issues for medicines for human use. It is expected for such work to be finalised before the end of this year.

#### ***Area of insufficiently developed fields of pharmacovigilance***

- Efforts have been undertaken to further strengthen pharmacovigilance in the areas of vaccines and paediatric medicines. This resulted in the availability of a guideline on paediatric pharmacovigilance and the current drafting of a guideline in relation to pharmacovigilance for vaccines.

### **III Priority Area: Further strengthening of the EU Pharmacovigilance System**

- During the reporting period work progressed in the field of work-sharing. Acknowledging that the EU Pharmacovigilance System is characterised by the availability of limited resources at the level of the Regulatory Authorities, the focus has been on the sharing of workload with respect to the assessment of Periodic Safety Update Reports (PSURs). A provisional list of EU Harmonised Birth Dates for active substances and PSUR Reference Member States was published. In addition, a Best Practice Guide for PSUR assessment was finalised. As regards the operational phase of the PSUR assessment work-sharing, such work-sharing will apply to the PSURs for all active substances included in the project with a data lockpoint after 31 May 2007.
- Since pandemic influenza has to be considered as an important threat to public health, various activities have been undertaken by the EU Regulatory System to adequately prepare, resulting in two major achievements in the context of pharmacovigilance/safety of medicines monitoring. Firstly an “EMEA Pandemic Influenza Crisis Management Plan for the Evaluation and Maintenance of Pandemic Influenza Vaccines and Antivirals” was finalised. Such document describes the management structures and the procedures which have been set up to respond rapidly and efficiently when a pandemic influenza crisis is announced. Secondly, the CHMP finalised recommendations for the

pharmaceutical industry in relation to the pharmacovigilance plan to be submitted as part of the risk management plan in the context of a marketing authorisation application for a pandemic influenza vaccine.

- Work has also started to develop an EU Regulatory System Incident Management Plan for medicines for human use. Building on the initiative undertaken by the EMEA in 1997, leading to the availability of a Crisis Management Plan for centrally authorised products, the need for a more global approach at EU level in relation to crisis management was identified, involving all medicinal products irrespective of the licensing route. This resulted in a discussion paper, setting out a number of key principles, which was agreed upon by Heads of Medicines Agencies during their February 2007 meeting. The next step will be the development of a detailed procedure which is expected to be finalised before the end of 2007.