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2008 Public Status Report on the Implementation of the European Risk Management Strategy

Executive Summary

The European Risk Management Strategy (ERMS) is a joint EMEA – Heads of Medicines Agencies (HMA) initiative to achieve high standards of public health protection for all medicines available on the European Union (EU) market¹. Improving the evidence for safety monitoring, a more proactive conduct of pharmacovigilance, and finding the right balance between timely access to medicines and the knowledge on the safety profile needed at the moment of licensing, are pivotal in order to enhance drug safety.

In December 2007 an ambitious two-year Work Programme to further progress the ERMS was launched. This public Status Report describes the achievements obtained in 2008. Overall, very good progress is noted on the further implementation of the ERMS, and progress occurs in various priority areas.

The 2008-2009 Work Programme focuses on the need to undertake further work in two fields: improving the operation of the EU Pharmacovigilance System, and strengthening the science and methodology that underpins the safety monitoring of medicines for human use. In both areas important achievements are noted and these are detailed in this Status Report. This progress has provided for a more efficient EU Regulatory System Network in the field of pharmacovigilance, has achieved a more intensive drug monitoring system, and allows pharmacovigilance to be conducted in the context of the benefit/risk concept applied throughout the lifecycle of medicinal products.

These achievements would not have been possible without an excellent collaboration between all EU Regulatory Authorities. The ERMS Facilitation Group, composed of Member States (Denmark (also Chair), France, Germany, Netherlands, Sweden and United Kingdom), European Commission and EMEA representatives, has been pivotal in taking this important project forward for the protection of public health.

¹ It should be noted that the ERMS applies to all European Economic Area (EEA) Countries.

2008 Progress on the Implementation of the European Risk Management Strategy

I Introduction

The document "Implementation of the Action Plan to Further Progress the European Risk Management Strategy: Rolling Two-Year Work Programme (2008-2009)" (Doc. Ref. EMEA/280089/2007), adopted by HMA at the November 2007 meeting, describes the further implementation of the ERMS to be undertaken in 2008 and 2009. In particular, it provides details on the key initiatives envisaged for the two-year period, which have been classified into two categories, i.e. further improving the operation of the EU Pharmacovigilance System, and strengthening the science and methodology that underpins the safety monitoring of medicines for human use.

This Progress Report provides details on the current status of implementation. Work done in 2008 has been grouped by priority area, as described below.

II Further Improving the Operation of the EU Pharmacovigilance System

Work undertaken in 2008 in this field related to the various priority areas identified in 2007, i.e. fully implementing and continuously monitoring current legislative provisions, addressing organisational aspects within the EU Pharmacovigilance System, whilst also strengthening quality assurance within the EU Regulatory System Network. In addition, improving transparency and communication should be a priority. Deliverables in 2008 in these areas are as follows:

Implementation and continuous monitoring of current legislative provisions

1. In relation to EudraVigilance and in particular the establishment of a fully operational system, a draft EudraVigilance Access Policy was released by the EMEA on 22 December 2008 for public consultation until 2 March 2009. Work also progressed as regards improving the quality of the data held in EudraVigilance whereby the EMEA has taken the initiative to launch in 2009 a call for tender process to address the EudraVigilance data quality management.
2. In order to address disharmony in the implementation of Community legislation in terms of national adverse reaction reporting requirements and procedures, two new sets of Q&A documents providing further guidance on pharmacovigilance requirements and procedures have been published in October 2008. These Q&A documents address frequently asked implementation questions from stakeholders in relation to Volume 9A of "The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use".
3. Major input was provided in the field of the international standardisation work (ISO/CEN/HL7) in relation to International Conference on Harmonisation (ICH) projects (i.e. E2 B(R3) and M5) as per the agreed action plan. The projects relate to individual case safety reporting and identification of medicinal products respectively. The EU Regulatory System Network was kept updated by the EMEA at regular intervals on progress made in order to further improve the understanding of the scope and implications of the international standardisation work and the process to be followed.

4. The introduction in 2005 of the novel concept of Risk Management Plans (RMPs) was the subject of continuous monitoring in 2008 through the Review and Learning project. Phases I and II of this project have been largely finalised with recommendations for future actions and development such as: (1) the revision of the Risk Management Guideline to take into account experience obtained and to include the consequences of new Community legislation (on Paediatrics and Advanced Therapies), (2) a mapping of implementation of RMPs in the Member States, and (3) the establishment of a dedicated drafting group to prepare recommendations on best practices, training and involvement of expertise in RMPs. Work is also being undertaken to evaluate short and long-term usefulness and effectiveness of RMPs.

Organisational aspects within the EU Pharmacovigilance System

5. In order to optimise the availability of limited resources within the EU Regulatory System Network, including its pharmacovigilance component, strategic discussions were held at HMA level, focusing on aspects such as available resources, development of resources, efficient and relevant use of resources. The outcome of these discussions has been summarised in information to HMA stakeholders.
6. Another important deliverable in the field of better deployment of available resources related to the further implementation of work-sharing in the area of Periodic Safety Update Reports (PSURs). Work in 2008 progressed very well, resulting in some 620 substances included in the scheme, the assignment to 24 Reference Member States and a first discussion of PSUR assessment reports under this new scheme at Pharmacovigilance Working Party (PhVWP) level. Another important output related to the publication of guidance for both pharmaceutical industry and assessors on the Co-ordination Group for Mutual Recognition and Decentralised Procedures (human) (CMD(h)) website in July 2008 and the organisation by the EMEA in December 2008 of training for assessors on PSUR assessment work-sharing.
7. Additional opportunities for work-sharing were also explored in 2008, primarily in the field of signal management, resulting in agreed (at HMA level) key principles of signal management in the EU and, in October 2008, the start of a pilot phase at the level of the PhVWP. Furthermore, HMA has requested the PhVWP to provide its perspective on the three top priorities for work-sharing.
8. Work within the frame of the Transatlantic Administrative Simplification exercise continued in 2008 and resulted in an Action Plan published on 17 June 2008. Pharmacovigilance related actions are collaboration on product specific RMPs and convergence of Risk Management formats.
9. In the field of "crisis" handling an EU Regulatory System Incident Management Plan for medicines for human use (irrespective of the licensing route) has been drafted. HMA agreed during the November 2008 meeting on the start of a pilot phase in 2009 to test the key principles and the procedure foreseen in this Incident Management Plan. Once this pilot phase has been concluded the Incident Management Plan will be revised taking into account experience obtained and will be subsequently made publicly available.
10. Work in the field of pandemic influenza preparedness continued in 2008 with deliverables such as the finalisation and publication of a core RMP for pandemic and pre-pandemic vaccines, and the launch of pilot testing of simplified PSURs to be used for pandemic and pre-pandemic vaccines during a pandemic.
11. Efforts to monitor compliance by Marketing Authorisation Holders (MAHs) with Community legislation and guidelines in the field of pharmacovigilance were directed to establishing an ad-hoc Pharmacovigilance Inspectors Working Group and agreement on deliverables such as the Pharmacovigilance Inspection Programme for Centrally Authorised Products (CAPs) up to 2011 and the procedure for the preparation of a risk-based programme for routine pharmacovigilance inspections of MAHs for CAPs.

Quality assurance within the EU Pharmacovigilance System

12. To further improve the quality of the work performed by regulators, initiatives continued to reinforce the quality assurance of the scientific review processes primarily in the field of risk management as part of the existing peer-review concept at Committee for Human Medicinal Products (CHMP) level.
13. In addition, work progressed in the field of strengthening the available scientific expertise made available by the National Competent Authorities (NCAs). Furthermore, a proposal was made for involvement of patients'/consumers' representatives in PhVWP meetings as observers in view of the launch of a 3 months pilot as of April 2009².

Transparency and communication on safety related aspects within the EU Pharmacovigilance System

14. Major work was undertaken to improve transparency in the field of the safety of medicines. A PhVWP survey on pharmacovigilance transparency and public communication policies in Member States was completed. It will now serve as a basis to develop proposals for transparency at the level of the PhVWP, the first focus being on the publication of the outcome of PhVWP discussions. Furthermore, a pilot was started on drafting Executive Summaries of Pharmacovigilance Assessment Reports which can then be made public. Both initiatives should, once implemented, lead to a greater transparency on the outcome of PhVWP discussions.
15. An important new tool to inform the EU Regulatory System Network on envisaged CHMP recommendations for regulatory action (based on identified safety concerns) and accompanied by communication to the general public (primarily in terms of EMEA Press Releases and Q&A documents) was introduced by the EMEA in February 2008. This early notification system has allowed the streamlining of communication on safety related aspects for medicines evaluated by the CHMP within the EU Regulatory System Network. Experience obtained so far is now being analysed in order to introduce any necessary improvements.

III Strengthening the Science and Methodology that Underpins the Safety Monitoring of Medicines for Human Use

Activities directed to apply a more proactive approach to the conduct of pharmacovigilance focused in 2008 on a wide range of initiatives. They included further improving the spontaneous reporting scheme, and moving-up the evidence hierarchy by generating more reliable pharmacoepidemiological data for pharmacovigilance purposes. Deliverables in 2008 in these fields are summarised below:

1. Work undertaken in the field of the EudraVigilance Datawarehouse and Analysis System (EVDAS), which is pivotal for signal detection on EudraVigilance data, allowed to further progress towards a fully available, reliable and high-performing system. In addition, discussions continued on the further development of EVDAS in the field of signal detection and data mining.
2. In the area of statistical signal detection methods a guideline on the use of such medicines was adopted by the CHMP in June 2008 and subsequently published. Furthermore, a retrospective study was performed by the EMEA on the validation of statistical signal detection for CAPs in EudraVigilance and the results were discussed at various (scientific) fora at the EMEA. Further research in this field will be undertaken by the EMEA and identified process improvements will be introduced. The results of this study will be published in 2009.

² This proposal was agreed upon by both HMA (January 2009) and the EMEA Management Board (March 2009).

3. Important progress was made as regards the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The current ENCePP “membership” totals 87 academic and research centres from 21 EEA countries. Efforts in 2008 focused on organisational aspects such as setting-up an ENCePP Implementation Advisory Group (ENCIAG) to help the EMEA create the network, and the establishment of 4 permanent Working Groups (looking at aspects such as research standards and accreditation, transparency and independence, data sources and methodologies, and an inventory of research centres). A Scientific Convention was held on 25 November 2008 on EU healthcare databases for pan-EU pharmacoepidemiological research, and a dedicated ENCePP webpage was launched by the EMEA at the end of 2008.
4. Progress in the research field was also achieved through the Innovative Medicines Initiative (IMI) with the participation of the EMEA and NCAs, alongside academic centres and other stakeholders, in calls for expression of interest. Furthermore, the CHMP and the PhVWP provided input to the third call under the 7th Framework Programme by proposing priority safety topics. The topic “Study of the arrhythmogenic potential of different classes of medicines” was included in the third call based on this input.
5. Activities to strengthen the methodology for benefit/risk analysis focused on how to improve the consistency, transparency and communication of benefit/risk assessment in CHMP Assessment Reports. Following public consultation a Reflection Paper on these aspects was adopted by the CHMP in March 2008 and subsequently made public. Two actions are currently being undertaken, i.e. a further revision of the CHMP Assessment Report template and the drafting of guidance for assessors with a view to roll-out and implement in June 2009. In parallel in September 2008 the EMEA launched a benefit/risk methodology project whereby in a first phase the different criteria currently used for drug evaluation amongst the European Agencies will be identified.
6. In the area of outcome evaluation existing initiatives, i.e. the Review and Learning project in the field of RMPs, continued and new projects have been announced by the EMEA (cfr. the 2009 EMEA Work Programme on methodology and outcomes assessment projects).
7. In 2008 preparatory work was undertaken for the implementation of the Advanced Therapies legislation. In this respect a Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products was adopted by the CHMP in November 2008 and came into operation on 31 December 2008.
8. Activities were expanded in 2008 in the frame of the pandemic influenza preparedness by further improving signal detection for vaccines through the establishment of specialist discussion fora. Likewise, a more proactive approach as regards pharmacovigilance for vaccines has been achieved through collaboration with the European Centre for Disease Prevention and Control (ECDC) in defining needs for data to improve the detection and investigation of adverse events following immunisation in the Member States, as well as consultation with the Food and Drug Administration (FDA) and selected Member States to explore the possibility of exchanging information on signals related to influenza data.