European Medicines Agency

Heads of Medicines Agencies

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Implementation of the Action Plan to Further Progress the European Risk Management Strategy: Rolling Two-Year Work Programme (2008–2009)

I Introduction

The 2005 document "Action Plan to Further Progress the European Risk Management Strategy", hereafter called "Action Plan", describes at a high-level how to achieve high standards of public health protection for all medicines available on the European Union (EU) market, which is the primary objective of the European Risk Management Strategy (ERMS).

In a report ("Public Status Report on the Implementation of the European Risk Management Strategy (Reporting Period Mid 2005 – Mid 2007"), published in July 2007, information is provided on all initiatives undertaken since mid 2005 up to the end of May 2007. The aim of the current document is to describe how the further implementation of the ERMS will be undertaken, by providing information on the initiatives envisaged for the period 2008-2009.

II Scope and Working Methodology

During the previous reporting period activities focussed, as per the "Action Plan", on three priority areas, i.e. the implementation of new Community legislation, complementary initiatives to arrive at the envisaged intensive drug monitoring system, and a further strengthening of the EU Pharmacovigilance System as part of the EU Regulatory System network. Although overall progress has been very good (cfr. "Public Status Report on the Implementation of the European Risk Management Strategy (Reporting Period Mid 2005 – Mid 2007)"), it needs to be acknowledged that progress in some areas has been more important than in other areas. In addition, there is a need to take due account of environmental changes which will impact on the further implementation of the ERMS.

Such environmental changes are:

- European Commission's Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance:

  Reference is made to the European Commission's announcement in February 2007 to strengthen medicines safety monitoring. Whilst one important pillar in the European Commission's Strategy refers to the need for changes to existing Community legislation, the European Commission has also emphasised that efforts should be undertaken to improve the implementation of the current legal framework.

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- Implementation of new Community legislation:

  The EU Regulatory System is being confronted with the implementation of two new important pieces of Community legislation, i.e. in the fields of paediatric medicines and advanced therapies. Especially in the field of advanced therapies a lot of preparatory work needs to be undertaken when implementing the new legal provisions in order to create an environment which provides for a safe use of these novel technologies.

- Transatlantic Administrative Simplification exercise:

  In the context of the "Framework for Advancing Transatlantic Economic Integration Between the European Union and the United States of America", agreed at the EU/US Summit on 30 April 2007, administrative simplification in the application of regulation of medicinal products will be promoted. Since the area of pharmacovigilance/safety of medicines is important in the framework of medicines regulation, it has been agreed to explore if administrative simplification can be achieved between the two regions in this field.

- Regulatory cooperation between the EU and non-EU Regulatory Authorities:

  Regulatory cooperation between the EU (European Commission and the EMEA) recently has been strengthened with both the US and the Japanese Health Authorities. As announced on 18 June 2007, current regulatory cooperation between the Food and Drug Administration (FDA) and the EU will be further expanded in several important areas. This will also relate to the field of safety of medicines, and an important topic in this respect will be the still novel concept of risk managements plans/RiskMAPs for the medicinal products covered by the EU/FDA Confidentiality Arrangements. On 2 February 2007 the EU and Japan (Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA)) concluded confidentiality arrangements in the area of human medicines regulation. Safety of medicines will also here become an important area for regulatory cooperation.

- EU Regulatory System Strategic Papers:

  Reference is made to both the EMEA Road Map and the Heads of Medicines Agencies (HMA) Strategy Paper. HMA adopted in February 2007 a revised Work Plan to implement their Strategy Paper. Whilst a number of recommendations focus on further improving patient safety, others relate to a further strengthening of the EU Regulatory System networking model, e.g. by reinforcing the involvement of HMA in regulatory activities undertaken at EU level. The EMEA is in the process of complementing its Road Map Implementation Plan with initiatives to be undertaken up to 2010.

The working methodology applied during the previous reporting period has proven to be appropriate. A targeted approach was applied in advancing the envisaged initiatives and best use was made of the available resources and established discussion fora, hence avoiding duplication of work. It needs to be acknowledged that the third pillar of the applied working methodology, i.e. involving all relevant stakeholders of the EU Pharmacovigilance System in the overall process, was not addressed to its full potential.

Therefore, the working methodology during this reporting period should be adapted to allow for more stakeholder involvement, whilst continuing giving priority to those initiatives which should most contribute to further improving patient safety. Stakeholders (e.g. patients, healthcare professionals, pharmaceutical industry, academia/learned societies) will be involved, where relevant, in the further development and implementation of the initiatives.

III Key Initiatives Envisaged During the Period Mid 2007 – Mid 2009

Taking into account the scope and working methodology, as described in Section II, various initiatives will be undertaken during the next two years. Some are initiatives which were planned during the previous reporting period but have not yet started or are still ongoing as a result of the aforementioned combination of a targeted approach and limited available resources. Other initiatives either had to be adapted because of recent developments, or have to be considered as new and additional to what was already planned in 2005. All envisaged activities should provide for a robust although challenging work programme for the next two years, but are considered necessary in order to provide an important contribution to the fulfilment of the requirements necessary to enhance drug safety in the 21st century (as already elaborated upon in the previous Work Programme), i.e.

- moving–up the evidence (best evidence concept);
- applying a more proactive conduct of pharmacovigilance;
- finding the right balance between timely access for patients to medicines and the knowledge needed on the safety profile of medicines at the moment of licensing, along with the most robust post-licensing programme.

The key initiatives that are envisaged for the reporting period 2008-2009 are described below. They have been classified into two categories, i.e. further improving the operation of the EU Pharmacovigilance System, and strengthening the science that underpins the safety monitoring of medicines for human use.

III.1 Further Improving the Operation of the EU Pharmacovigilance System

An efficient operation of the EU Regulatory System networking model, and in particular its pharmacovigilance component, is vital in order to adequately handle safety concerns for medicinal products for human use, both in the pre- and the post- authorisation phase. The European Commission's "Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance" has indicated the need to improve the implementation of the current legislative framework in which the EU Pharmacovigilance System operates. Four aspects will need ongoing particular attention during the next phase of the ERMS implementation, i.e. the implementation of current Community legislation and its continuous monitoring, the organisation of the EU Pharmacovigilance System, quality assurance within the EU Pharmacovigilance System, and transparency and communication aspects within the networking model.

Fully implementing and continuously monitoring current legislative provisions

Although important progress has been made during the previous reporting period (mid 2005 – mid 2007) in relation to the implementation of the 2005 Community legislation, there is still ongoing work, primarily as regards a fully operational EudraVigilance system and a strengthening of transparency in the field of safety of medicines. Furthermore, an efficient implementation can only be achieved if adequate monitoring is in place and correctives measures are being applied, when considered necessary. Particular emphasis will be put on the risk management plan concept as it is an important tool for proactive pharmacovigilance. The Review and Learning project will be broadened to also investigate the impact of risk management plans (with particular focus on the harmonised implementation of risk minimisation measures across the EU and the appropriateness of the agreed post-authorisation safety studies). Regular feedback from stakeholders is paramount for achieving an efficient implementation of the 2005 legislative provisions.

Key initiatives

- Establishing a fully operational EudraVigilance system in the field of medicines for human use by addressing
  - identified areas of disharmony in the implementation of Community legislation, in terms of national adverse reaction reporting requirements and procedures, and
  - non-adherence to the expedited reporting requirements and the agreed reporting principles

  (cfr. also the attached "Action Plan Addressing the Areas of Disharmony in the Implementation of Community Legislation and the Impact on the Establishment of a Fully Operational EudraVigilance System in the Field of Medicines for Human Use", as agreed upon by both Heads of Medicines Agencies and the EMEA Management Board during the first half of 2007).
- Providing appropriate levels of access to EudraVigilance data to the various stakeholders.
- Contributing to the ongoing international standardisation work in relation to ICH E2B (R3) and M5.
- Updating Annex 6 (Distribution Requirements and Address Lists for Data Submission) of Volume 9A of "The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use" in line with the European Commission's Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance, as announced in February 2007.
- Monitoring the implementation of the various legal tools introduced in 2005, e.g. in relation to the concept of risk management plans, and taking remedial actions, whenever needed, after consultation with the relevant stakeholders.

Addressing organisational aspects within the EU Pharmacovigilance System

An adequate organisation of an increasingly complex EU Regulatory System (consisting of 27 Members States and 3 European Economic Area (EEA) Countries) is an important prerequisite in order to achieve a smooth functioning and an efficient operation of the networking model. Various aspects need to be considered in this respect, ranging from an increasing workload to be handled in sometimes very tight timeframes by limited resources, the need to continuously provide training for regulators to keep abreast of new scientific and technical developments, adequate crisis management, etc. Furthermore, initiatives undertaken by the European Commission to provide for better regulation and to reduce administrative burden will need to be taken into account.

Key initiatives

- Optimising the availability of limited resources within the EU Regulatory System, and in particular its pharmacovigilance component, by
  - performing adequate workload and resource planning (within the frame of the activities undertaken at the level of the HMA Resources Planning Group), and

Key initiatives

- fully implementing established work-sharing concepts (i.e. in the field of Periodic Safety Update Reports (PSURs)) and exploring additional opportunities for work-sharing (e.g. in the context of the "Action Plan Addressing the Areas of Disharmony in the Implementation of Community Legislation and the Impact on the Establishment of a Fully Operational EudraVigilance System in the Field of Medicines for Human Use", or in other fields such as signal detection through the EudraVigilance Datawarehouse and Analysis System (EVDAS)).

- Progressing work within the frame of the Transatlantic Administrative Simplification exercise (pharmacovigilance related aspects) in accordance with the agreed Action Plan.
- Establishing a Competence Development Programme for regulators within the EU Pharmacovigilance System in the context of the activities undertaken by the HMA Training Project Team.
- Finalising the development of an EU Regulatory System Incident Management Plan for medicines for human use, implementing and testing it at regular intervals, and subsequently introducing any necessary amendments taking into account lessons learnt.
- Strengthening the pandemic influenza preparedness by testing at regular intervals the available crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals.
- Strengthening the interaction with the World Health Organisation (WHO) in various aspects of pharmacovigilance and reflecting such strengthening through a revision of the document "Principles of Collaboration with the World Health Organisation in Matters of International Pharmacovigilance", included in Volume 9A of "The Rules Governing Medicinal Products in the European Union - Guidelines of Pharmacovigilance for Medicinal Products for Human Use".
- Monitoring compliance by Marketing Authorisation Holders with Community legislation and the guidelines included in the aforementioned Volume 9A.

Strengthening quality assurance within the EU Pharmacovigilance System

It is paramount to build a culture of continuous improvement into the quality of the work performed by regulators. In order to achieve this objective the Benchmarking of European Medicines Agencies (BEMA) initiative was launched by the EU Regulatory System. Activities during the next reference period will focus on making available top quality scientific expertise to the EU Regulatory System, in particular the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Working Party (PhVWP), reinforcing and expanding the existing peer review concept, etc.

Key initiatives

- Enhancing the overall quality of the EU Pharmacovigilance System by ensuring the availability at EU level of top quality scientific expertise through the development of an EU-wide up-to-date inventory of the available scientific expertise (including expertise from academia/learned societies and non-EU Regulatory Authorities).

Key initiatives

- Reviewing the composition of both the CHMP and the PhVWP as a consequence of the new three years' mandate of their members, with the aim of reinforcing the scientific expertise, taking into account the outcome of a gap-analysis of the available expertise, and providing for any additional specialist input, whenever needed, in order to better support the CHMP and the PhVWP in the execution of their scientific assessment work.
- Reinforcing the quality assurance of the scientific review processes by
  - further improving the existing peer review system for the scientific work undertaken at CHMP level in the pre-authorisation phase, and
  - exploring an extension of the peer review concept to the post-authorisation phase, both in relation to the CHMP and the PhVWP activities, taking due account of experience gained with the current peer review arrangements in the pre-authorisation phase.

Improving transparency and communication on safety related aspects within the EU Pharmacovigilance System

It needs to be acknowledged that there is an increasing call for more transparency as regards the work undertaken by Regulatory Authorities. This certainly is the case in the field of safety of medicines. Two aspects need to be considered in this respect, the overall transparency on the handling of safety issues and the routine provision of information, as well as effective and timely risk communication. Initiatives, which will complement current legislative provisions, will address both aspects.

Key initiatives

- Increasing the transparency in the field of safety of medicines for human use by
  - developing a dedicated Q&A document explaining the operation of the EU Pharmacovigilance System, including the roles and responsibilities of all involved parties,
  - providing better targeted and more timely pharmacovigilance related information, and
  - developing a policy on the publication of the scientific rationale for opinion-making (to allow for better targeted and more timely information on the opinion-making, including the rationale) and subsequently implementing such policy.
- Improving the communication on safety related issues by finalising the development of an EU Regulatory System Communication Strategy on emerging safety related issues for medicines for human use (including external consultation with the various stakeholders) and subsequently implementing such Strategy within the networking model, including evaluation of its efficiency.

III.2 Strengthening the Science and Methodology that Underpins the Safety Monitoring of Medicines for Human Use

A robust scientific assessment, in particular as regards the risks associated with the use of a medicinal product, is paramount in order to obtain a clear picture on the medicine's safety profile. Strengthening the science that underpins the safety monitoring of medicines, needs, however, always to be put into the context of the

benefit/risk concept, whereby the overall aim is to continuously evaluate the benefit/risk balance of a medicine throughout its entire lifecycle. In addition, there is also a need to progress work on methodological aspects. Efforts to strengthen both areas will focus over the next two years on several topics, such as the data resources, the scientific tools, research aspects, etc.

The spontaneous reporting scheme will remain one of the corner stones of the pharmacovigilance system and, therefore, initiatives in this field will relate to further improving it. The further development and the full implementation of EudraVigilance, which should lead to a better use of the database and its functionalities, should provide an important contribution to an improved conduct of pharmacovigilance at EU level.

Acknowledging the importance of the spontaneous reporting concept, there is, however, a need to further increase the knowledge and to move-up the evidence. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is being established in order to provide an important contribution to the best evidence concept by generating more reliable pharmacoepidemiological data for pharmacovigilance purposes. Alongside ENCePP, investing in research (through the Innovative Medicines Initiative (IMI) and the Health Theme of the 7th Framework Programme) will be equally important to allow for a more proactive conduct of pharmacovigilance.

Finally, there is also a need to adequately prepare for the implementation of the new Advanced Therapies legislation. New challenges stemming from such legislation will require new scientific approaches into the understanding of risks associated with emerging therapies.

Key initiatives

- Providing for a full roll-out EVDAS and making available detailed guidance on the use of statistical signal detection methods in EVDAS.
- Further developing EudraVigilance by introducing additional functionalities, especially in the field of signal detection and data mining.
- Further developing ENCePP, building on the important progress already achieved during the previous reporting period, hereby maintaining and even further strengthening the active interface with academia/learned societies and implementing such network in order to broaden the access to and optimising the use of pharmacoepidemiology resources.
- Contributing to IMI in the field of pharmacovigilance, especially in relation to studies to be performed as regards the methodologies to conduct pharmacovigilance and the development of new data resources as well as the strengthening of existing ones.
- Contributing to the Health Theme of the 7th Framework Programme, in particular by identifying important public health issues in drug safety affecting groups/classes of medicines including off-patent products, and providing such information to the responsible European Commission Services in the context of future calls for proposals.
- Exploring other methods of risk detection by taking due account of similar initiatives undertaken by EU and non-EU Regulatory Authorities.

Key initiatives

- Further improving opinion-making within the EU Regulatory System, building on the activities already undertaken at CHMP level by
  - integrating the most useful features of benefit/risk assessment models and methods into CHMP guidelines and assessment report templates, and
  - further investigating the methodology of benefit/risk assessment.
- Undertaking outcome evaluation by
  - developing and subsequently implementing methods to monitor the outcome of regulatory action, and
  - assessing the impact of regulatory action and taking corrective measures, whenever needed.
- Preparing for an adequate implementation of the Advanced Therapies legislation by drafting guidance in the fields of post-authorisation follow-up of efficacy, adverse reactions and risk management.
- Expanding activities in the frame of the pandemic influenza preparedness by
  - looking into signal detection aspects with a view to strengthening the review of adverse reaction data related to the use of influenza vaccines, and
  - providing recommendations (working in close collaboration with WHO) to the pharmaceutical industry in relation to risk management planning for influenza vaccines used in a pre-pandemic situation.
- Exploring if additional activities need to be undertaken in order to achieve a more proactive approach in some specific areas, such as paediatric pharmacovigilance and pharmacovigilance for vaccines (as regards the latter, in close cooperation with the European Centre for Disease Prevention and Control (ECDC)).

IV Reporting

Information on the follow-up to all initiatives will be provided in a yearly Status Report which will be made publicly available. In addition, in order to strengthen the interaction with stakeholders, a yearly workshop will be jointly organised by the EMEA and HMA with representatives of patients, healthcare professionals and pharmaceutical industry, to discuss progress made and look into work still to be undertaken. This should allow for better active involvement of such stakeholders in the further development and implementation of the ERMS.