already having an effect on research in the UK – ethics committee submissions are down this year.

Clearly with pharmacogenetics we are looking at a static end-point. That is, a germline polymorphism will be present from birth to death. However, our cells, organs and the body represent dynamic systems which are constantly changing and adapting to the environment. Therefore any response to a drug may also have to take account of these processes. Again, technologies are available here. To look at protein patterns in the body, we can use proteomic technologies, while metabonomics looks at the pattern of metabolites in body fluids and how they change in response to drugs. Let me give you an example of the potential power of the latter: in patients with IHD, it was possible through analysis of metabolite patterns in human serum, to distinguish between patients with normal coronary arteries and those with triple vessel disease with a specificity greater than 90%. That is a very impressive result and highlights the potential power of the technique.

We are developing all these technologies, and there is no doubt that they are getting cheaper. However, for them to be successful, they need to be easily incorporated into current clinical practice. They need to be amenable to the general practitioner who has 7 min to see a patient, and cannot possibly be expected to become an expert in all aspects of human genetics. This brings me back to the power and usefulness of information technology. We are going to generate a lot of data with these biotechnologies – let me give you an example: currently there are gene chips with which you can simultaneously look at 500,000 gene variants. Potentially this will provide you with 500,000 data points on each individual. If you are doing a study in 1000 patients, for example to identify predisposing factors, 5×10^8 data points. Such data will need to be gathered, harnessed, and interpreted. This field of bioinformatics is therefore

going to be absolutely crucial. Data that is gathered through these technologies will have to be translated into a form that is understandable by the prescribing clinician. This will require the linkage between bioinformatics and health informatics, and as you can imagine, this in itself is going to be a major challenge.

Ladies and Gentleman. To conclude.

I have given you a brief tour of the problems that we are currently facing with respect to drug safety issues. For the future, we need to embrace all the available and the emerging technologies so that we can make drug therapy as safe as possible and thereby protect public health. However, it is not going to be easy. There are many obstacles to be overcome, some of which I have gone through. In the end, this is going to require a concerted effort from all stakeholders including patients. The sooner we begin to tackle these issues, the quicker we will get there. Thank you for your attention.

参考4

European Medicines Agency

HMA
Heads of Medicines Agencies

London, 26 July 2007
Doc. Ref. EMEA/308167/2007

European Risk Management Strategy: Achievements to date

Reviewing the status of implementation of the European Risk Management Strategy (ERMS) during their meeting in Lisbon on 10 July 2007, the European Medicines Agency (EMEA) and Heads of Medicines Agencies (HMA) expressed their satisfaction with the progress made to date and had a first discussion on the priority areas for the next two years.

No effective medicine is without risk and the benefits of a medicinal product always need to be balanced against its risks. While it is acknowledged that medicines regulation cannot protect the public from every risk, the ERMS aims to provide for a more coherent approach to the detection, assessment, minimisation and communication of risks of medicines in Europe. This should lead to a more proactive approach to safety monitoring of medicines throughout their life-cycle.

Achievements to date

Achievements made between 2005 and 2007 are described in the 'Public Status Report on the Implementation of the European Risk Management Strategy'. Some of the achievements have been:

- Implementing the legal tools for monitoring the safety of medicines and for regulatory actions provided for by revised EU pharmaceutical legislation, with particular emphasis on the systematic implementation of risk management plans;
- Strengthening the spontaneous reporting scheme through further improvements to implementation of electronic reporting of adverse drug reactions to the EudraVigilance database;
- Launching the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) project to strengthen the monitoring of medicinal products by facilitating the conduct of multi-centre post-authorisation safety studies;
- Contributing, in collaboration with the European Commission, to the conduct of research in the field of pharmacovigilance and safety of medicines in the context of the Health Theme of the 7th Framework Programme;
- Strengthening the organisation and the operation of the EU Pharmacovigilance System.

Priority areas for the next two years

Building on the achievements to date, the EMEA and HMA are in the process of finalising a work programme on activities to be undertaken over the next two years to further implement the ERMS. A number of environmental changes will impact on this work programme, such as the European Commission's Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance. Two main areas will be covered by the ERMS during the next two years: further improving the operation of the EU Pharmacovigilance System and strengthening the science that underpins the safety monitoring of medicines for human use. It is envisaged for this work programme to be published following the November 2007 HMA meeting.

-- ENDS --

Notes:

1. In autumn 2002, the Heads of Medicines Agencies (HMA) agreed on the outline of a European Risk Management Strategy (ERMS). A summary report prepared by the HMA Ad Hoc Working Group on ERMS was subsequently published in January 2003

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(MCA/PL/JM/HoASummaryReport.doc on http://heads.medagencies.org). The aim of the ERMS is to strengthen the safety monitoring in the EU of medicinal products for human use.

2. The 'Public Status Report on the Implementation of the European Risk Management Strategy' is available on the EMEA website.
3. The final version of the work programme to further implement the ERMS in the next two years will be presented at the November 2007 Heads of Medicines Agency Meeting.
4. The European Commission's Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance can be found at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm
5. This press release, together with other information on the work of the EMEA, can be found on the EMEA website: www.emea.europa.eu

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European Medicines Agency

HMA
Heads of Medicines Agencies

London, 26 August 2007
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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 form 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.

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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, primarilay 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 2nd 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 7th 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.

European Medicines Agency

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Annex 1

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.

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- 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 2nd 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 7th 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 7th 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

pharmacaceutical 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.

参考6

European Medicines Agency

HMA
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.

参考7

European Medicines Agency

HMA
Heads of Medicines Agencies

London, 20 December 2007
Doc. Ref. EMEA/564868/2007

European Risk Management Strategy: 2008-2009 work programme adopted

The Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMEA) agreed on a rolling two-year (2008-2009) work programme to further progress the European Risk Management Strategy (ERMS) at their November 2007 meeting in Funchal (Portugal).

No effective medicine is without risk and the benefits of a medicinal product always need to be weighed up against its risks. The challenge for regulators is to find the right balance between timely availability of new medicines and the fact that knowledge on the safety profile is limited at the time of marketing authorisation. The ERMS aims to provide for a more proactive conduct of pharmacovigilance by putting in place measures that allow for the early detection, assessment, minimisation and communication of risks of medicines in Europe throughout their lifecycle.

The ERMS workprogramme during the next two years will focus on two areas: 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.

Some of the key initiatives, which aim to improve the implementation of the current legal framework, relate to:

- Further developing the EudraVigilance system through the introduction of additional functionalities, hence leading to a fully operational system
- Optimising the functioning of the EU Regulatory System Network, and in particular its pharmacovigilance component
- Reinforcing operational and scientific quality assurance
- Increasing transparency and improving communication on the safety of medicines
- Implementing the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) project in order to broaden the access to and optimise the use of pharmacoepidemiology resources
- Exploring methodologies in the conduct of pharmacovigilance

The activities to be undertaken over the next two years build on the progress already made, but also take into account a number of environmental changes which will impact on the implementation of the ERMS, such as the European Commission's Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance, the implementation of new European Union (EU) legislation on paediatric medicines and on advanced therapies, and the increased regulatory cooperation with non-EU regulatory authorities.

-- ENDS --

Notes:

1. In autumn 2002, the Heads of Medicines Agencies (HMA) agreed on the outline of a European Risk Management Strategy (ERMS). A summary report prepared by the HMA Ad Hoc Working Group on ERMS was subsequently published in January 2003 (MCA/PL/JM/HoASummaryReport.doc on http://heads.medagencies.org). The aim of the ERMS is to strengthen the safety monitoring in the EU of medicinal products for human use by providing for a more coherent approach to the detection, assessment, minimisation and communication of risks of medicines.

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2. The rolling Two-Year Work Programme (2008-2009) to further progress the ERMS is available here: http://www.emea.europa.eu/pdfs/human/phv/28008907en.pdf
3. A 'Public Status Report on the Implementation of the European Risk Management Strategy', published in July 2007, is available on the EMEA website here: http://www.emea.europa.eu/pdfs/human/phv/16895407en.pdf
4. The European Commission's Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance can be found at: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm
5. This press release, together with other information on the work of the EMEA, can be found on the EMEA website: www.emea.europa.eu

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