European Medicines Agency

Heads of Medicines Agencies

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Action Plan
to
Further Progress the European Risk Management Strategy

I Introduction

In Autumn 2002 the Heads of Medicines Agencies (HMA) agreed on the outline of an 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 HMA initiative took into account the work undertaken by the European Medicines Agency (EMEA) in Spring 2002 on the establishment of an EMEA Risk Management Strategy.

The aim of the ERMS is to:
(1) build on National Competent Authorities' (NCAs) resources and expertise, whilst incorporating the EMEA's role in the co-ordination of the supervision of products authorised in the European Union (EU),
(2) support consistent, robust decision-making,
(3) ensure accessible information on safety, including information exchange between all EU Competent Authorities,
(4) reduce reduplication of work, and
(5) be demonstrably effective in protecting public health.

Five key priorities for initial action were agreed, i.e. to
(1) review the mandate of the Pharmacovigilance Working Party (PhVWP),
(2) conduct a high level survey of EU pharmacovigilance resources,
(3) make proposals to strengthen pharmacovigilance communications and information exchange,
(4) secure the best use of scarce resources for pharmacovigilance, and
(5) provide guidance on Risk Management Plans.

A report of the Ad Hoc Working Group on the progress of the implementation of the ERMS is now available. Taking into account the current status of the ERMS, the EMEA and HMA have identified the need to progress further such strategy, building on the achievements already attained.

The aim of this Action Plan is to provide a high-level overview of the various actions the EMEA and HMA wish to undertake over the next few years in the field of risk management, hence contributing to the safe and effective use of medicines and the overall promotion and protection of public health. A continuous monitoring of the further implementation of the ERMS will allow HMA and the EMEA to take any additional initiatives, whenever necessary.

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HMA and the EMEA wish to underline that Regulatory Authorities are only one element of the Regulatory System and that the contribution of all other stakeholders to the safe and effective use of medicines is paramount to achieve an adequate protection of public health.

II Outline of the Second Implementation Phase

II.1 Rationale of the Second Implementation Phase

Whereas the first implementation phase, covering the period 2003-2004, mainly concentrated on a further improvement of the operation and organisation of the pharmacovigilance elements of the EU Regulatory System, as well as the introduction of further improvements in the spontaneous reporting scheme, the work already undertaken has demonstrated a better ability of the EU Pharmacovigilance System to ensure adequate monitoring of the medicinal products available on the EU market.

Although good progress has already been made in relation to the implementation of the agreed ERMS, there are still a number of outstanding actions which require follow-up. As indicated in the progress report of the Ad Hoc Working Group on the implementation of the ERMS, not yet completed work relates to the initially agreed five key priorities. In summary, improving organisational and operational aspects of the EU Regulatory System (e.g. by strengthening the operation of the PhVWP, by developing further work sharing arrangements and establishing more partnering arrangements), speeding-up the population of the EudraVigilance system and further developing it, and widening information sharing arrangements with other regions irrespective of the licensing route, should be key areas in the next implementation phase of the ERMS.

In addition, recent events, both in terms of strategic developments (e.g. the publication of the EMEA Road Map to 2010, and the development of an HMA Strategy on the Future European Medicines Regulatory Network), legislative initiatives (new Community and national legislation in the pharmaceutical field) and emerging safety issues for high-profile medicines (e.g. COX-2 medicines and SSRIs), necessitate further development of the 2003 ERMS, resulting in a number of complementary initiatives which should be undertaken.

The successful implementation of the revised 2003 ERMS should allow Regulatory Authorities to provide an important contribution to the further improvement of patient safety, a need which was also recently identified in the "Luxembourg Declaration on Patient Safety".

II.2 Scope of the Second Implementation Phase

When defining the scope of the second implementation phase one needs to take into account:

(1) the not yet available deliverables stemming from the 2003 ERMS, and
(2) the need to complement the initiatives identified in the 2003 ERMS further to recent developments in terms of strategic initiatives such as the EMEA Road Map project, changes of a legislative nature (new Community and national legislation in the area of medicines) and emerging safety issues for high-profile medicines.

It needs to be emphasised that even in a changing environment the overall objectives of the 2003 ERMS still remain valid, i.e. to achieve high standards of public health protection for all medicines, regardless of the route of authorisation,

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and to further develop the collaborative approach to maximise use of resources available at EU level, recognising that all Competent Authorities have a role to play.

However, in view of the increasing and justified demands from patients and the general public for an adequate protection of public health, resulting in the availability of safe and effective medicines, it is important to re-emphasise that the concept of "zero risk" does not apply to medicinal products. The licensing of medicinal products needs to be assessed in the context of the benefit/risk balance concept, whereby demonstrated benefits must outweigh known risks, leading to a favourable benefit/risk ratio and the resulting marketing authorisation.

It needs to be stressed that even with the best knowledge of medicines at the moment of licensing (in terms of quality, safety and efficacy), adverse drug reactions which were not predictable or detectable pre-authorisation, will occur post-licensing when medicines are increasingly used in real life situations. Therefore, the ultimate aim of the ERMS is to further improve patient safety by creating an adequate framework which strikes the right balance between timely access for patients to medicines and the knowledge needed on the safety profile of a medicine at the moment of licensing, along with the most robust post-licensing programme.

The new legislative tools, as well as the complementary initiatives that the EMEA and HMA wish to undertake, as elaborated below, will not lead to an increase of the pre-authorisation regulatory data requirements. Instead, they will create an environment which is conducive to timely access to new safe and effective medicines, sometimes tested in small numbers of patients, with a strengthening of the post-authorisation risk management.

III Identification of the Priority Areas and the Actions for the Second Implementation Phase

As outlined above, the second implementation phase of the ERMS will concentrate on meeting the aim of providing a framework which allows for the best protection of public health, underpinned by an increasingly proactive approach by the EU Regulatory Authorities towards the identification and handling of safety concerns both pre- and post-licensing of medicines, and applying in all scientific considerations the concept of benefit/risk, as enshrined in Community legislation. The initiatives to be taken during the second implementation phase will relate to three priority areas, i.e. the implementation of new Community legislation, complementary implementing 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.

III.1 Implementation of New Community Legislation

New Community legislation, coming into force in November 2005, is a translation of the need identified by the European Commission, the European Parliament and the Council to further strengthen the safety monitoring of medicinal products. The new legislative provisions will allow for an intensive supervision of the undesirable effects of medicines in order to take appropriate regulatory action, including, where needed, a rapid withdrawal from the market of any medicinal product presenting a negative benefit/risk balance under normal conditions of use.

Hence, new Community legislation will introduce additional tools to complement the existing legislative requirements. The toolkit comprises:

(1) the submission by pharmaceutical companies of risk management plans in the context of marketing authorisation applications,

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(2) the collection of specific pharmacovigilance data for centrally authorised products from targeted groups of patients,
(3) the possibility for Regulatory Authorities to take urgent provisional measures, for instance as a result of the evaluation of pharmacovigilance data,
(4) a reinforcement of the benefit/risk balance concept in the scientific assessment throughout the life cycle of medicines,
(5) a revision of the PSUR periodicity,
(6) a mandatory electronic reporting, save in exceptional circumstances, of Adverse Drug Reactions (ADRs) by the NCAs and the pharmaceutical industry, and
(7) a strengthening of the enforcement through the possibility for financial penalties for pharmaceutical companies in case of non-adherence to the legal obligations.

In summary, these tools aim for an adequate protection of public health, whilst not delaying the timely access to medicines for patients.

In addition, several new legislative provisions will result in increased transparency in the field of the safety of medicines through:
(1) the timely provision of targeted pharmacovigilance related information to healthcare professionals and the general public, and
(2) the accessibility of the EudraVigilance database to healthcare professionals and the general public, with appropriate levels of access being provided, whilst fully respecting the confidentiality of personal data.

The adequate implementation of an effective communication on pharmacovigilance/safety related issues to healthcare professionals and the public will require a very close collaboration between the EMEA and the NCAs.

The EMEA and HMA are currently preparing for the timely implementation of all new legislative provisions, resulting in the development of the necessary guidance documents for the EU Regulatory Authorities, for pharmaceutical industry and other stakeholders.

III.2 Complementary Implementing Initiatives to Arrive at the Envisaged Intensive Drug Monitoring System

In addition to an adequate implementation of new Community legislation, complementary implementing initiatives will be undertaken to arrive at the envisaged intensive drug monitoring system. Such initiatives will relate to the different fields of risk management, i.e. risk detection, risk assessment, risk minimisation and risk communication. Furthermore, particular attention will be given to insufficiently developed fields of pharmacovigilance. These complementary initiatives should further contribute to the promotion of the safe use of medicines and the prevention of adverse drug reactions. The implementation of these complementary initiatives will take due account of the work recently undertaken by the EMEA/CHMP Working Group with Patients Organisations. The final recommendations and proposals for action stemming from this Working Group (EMEA/CHMP Working Group with Patients Organisations – Outcome of Discussions: Recommendations and Proposals for Action, Doc. Ref: EMEA/149479/2004 Final) in the area of pharmacovigilance address issues such as transparency and communication, improved reporting, active pharmacovigilance methods and pharmacovigilance planning. Some of these recommendations require a harmonised approach at EU level before implementation.

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Different Fields of Risk Management

Risk Detection

Currently available data sources mainly come within the context of the spontaneous reporting scheme. The spontaneous reporting system has for several decades been the cornerstone of the surveillance of medicinal products. Although it has allowed Regulatory Authorities to act on the findings to protect public health, it is increasingly recognised that in its current form it has its limitations. Since the expedited reporting by healthcare professionals in several Member States is still of a voluntarily nature, the levels of reporting by such healthcare professionals are quite variable. In addition, experience has shown that for specific safety concerns the spontaneous reporting system does not seem adequate to provide the best evidence needed for robust decision-making.

Therefore, complementary implementing initiatives in the field of risk detection aim to create a framework which allows the earliest possible detection of important safety signals. A more efficient use of the EU pharmacovigilance network in all its aspects will be paramount to meet such aim. Since current data gathering has its limitations, moving-up the "evidence hierarchy" in order to have access to the best evidence will be the main challenge EU Regulatory Authorities will have to face.

Consequently, actions will focus on making better use of the wide variety of sources of evidence, and in particular target improvements to the spontaneous reporting scheme and a strengthening of the active surveillance methods.

Depending on the initiatives already undertaken at national level, the range of actions in relation to the spontaneous reporting system will include:

(1) widening the involvement to all healthcare professionals (specifically targeting spontaneous reporting in the hospital setting) and to patients,
(2) establishing adequate educational programmes (e.g. on ADR reporting) resulting in a process of continuing education of healthcare professionals,
(3) providing feedback to and entering into a dialogue with the reporters, and
(4) facilitating reporting through initiatives such as introducing the concept of electronic reports (building on initiatives already undertaken within the context of the EudraVigilance project), allowing reporting through dedicated phone numbers, etc.

Another important area with respect to spontaneous reporting relates to the EudraVigilance project. The main focus over the next few months will be:

(1) speeding-up the implementation at the level of both the NCAs and the pharmaceutical industry,
(2) adequately addressing the identified horizontal issues resulting from the individual implementation meetings with the NCAs,
(3) implementing the consensus reached at HMA level as regards the follow-up to the identified policy, compliance and regulatory aspects resulting from first experience with electronic reporting, and
(4) further developing the EudraVigilance database by introducing additional functionalities (e.g. in order to achieve the best tools for signal detection and data mining).

Intensive drug monitoring will require in addition to a strengthening of the spontaneous reporting system, the availability of additional sources of pharmacovigilance information. Important tools to further strengthen the best evidence approach in pharmacovigilance and risk management are the conduct of well-designed epidemiological studies and other methods of active surveillance to investigate and quantify the risks. Also data sources such as population-based databases (whereby the feasibility of combining such databases will be investigated) and usage/utilisation data will be increasingly used to strengthen patient safety.

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A successful implementation of the best evidence concept will, however, necessitate a targeted approach. The identification of medicines requiring intensive monitoring will be a first prerequisite, followed by publication of such a list to improve transparency in this field. In parallel, academic centres to be involved in intensive monitoring of targeted medicines will be identified, followed by the development of a network of such centres to allow subsequent practical implementation. In addition, the funding through the 7th Framework Programme of research into the development of novel methodologies (such as risk minimisation methodologies, methodologies to link clinical trial safety data with post-authorisation safety data, methodologies to link spontaneous reporting data with epidemiology or population data) will be explored.

Risk Assessment

Actions which will be undertaken in the field of risk assessment will focus on further organisational and operational improvements of the EU Regulatory System, taking into account the achievements attained at the end of the first implementation phase, and better methodologies underpinning the benefit/risk analysis.

In order to achieve robust decision-making across the EU, irrespective of the licensing route of medicines, the functioning of both the EMEA Committee for Human Medicinal Products (CHMP) and the PhVWP (with its dual reporting line to the CHMP and the NCAs) will be further improved, leading to increased quality, as well as scientific and regulatory consistency of the scientific evaluation processes. The concept of peer review during the scientific assessment will be strengthened and more use will be made of specialised expertise during the review process. Making the best use of the revised mandate of the PhVWP, as well as an adequate functioning of the newly established Coordination Group will be extremely important in order to arrive at timely outputs implemented in all Member States.

Another important aspect to be considered with a view to strengthening the consistency of decision-making will be an improvement of the methodology for benefit/risk analysis, leading to a more systematic approach. Identification, characterisation and quantification of the risks to consider the use of the most adequate risk minimisation measures, will be important elements to be taken into account.

Risk Minimisation

The implementation of the new legislative provisions in the area of risk minimisation mainly concentrates on the introduction of the concept of risk management plans provided by pharmaceutical companies as part of their applications for marketing authorisation. The most important challenge for EU wide authorised medicines in this respect will be the practicability of implementation of the risk minimisation tools across the EU. First experience obtained with this novel concept will allow as a next step to further develop it in order to arrive at a real Risk Minimisation Toolbox, characterised by reliable tools with measurable effects and criteria for their use.

This second phase will require that work will be started to measure the effects of these risk minimisation tools. Likewise, once regulatory action has been taken on the basis of the outcome of the scientific assessment, it is important to monitor the implementation of such outcome and to measure the impact of the regulatory decision. Possible areas could be how pharmaceutical companies comply with the implementation of important variations to marketing authorisations, e.g. Urgent Safety Restriction (USR) procedures.

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Risk Communication

Additional initiatives in the field of risk communication will focus on achieving effective communication between all Competent Authorities since this is a prerequisite for timely action on safety issues and a successful implementation of the agreed regulatory action.

In addition, efforts will be undertaken to improve the communication between Regulatory Authorities and pharmaceutical industry, leading to the development of a Code of Conduct which should facilitate such communication process.

Furthermore, initiatives will be taken to establish adequate mechanisms to effectively deal with communication on safety issues in case of crisis situations.

In order to meet the objective of effective and timely risk communication, discussions with all stakeholders, including healthcare professionals and patients, will be initiated on the aspects of communication and provision of information on safety related issues with a view to arriving at a common approach at EU level, resulting in the availability of an EU Strategy in this field.

In parallel, discussions will be started on how to further improve transparency in the field of safety information. These discussions will not only relate to the implementation of new Community legislation, but will widen to what additional actions can be undertaken (e.g. making available outcomes of discussion at the level of the PhVWP).

Insufficiently Developed Fields of Pharmacovigilance

A number of insufficiently developed fields of pharmacovigilance can be identified, such as the areas of paediatric pharmacovigilance and vaccines.

The field of paediatric pharmacovigilance requires particular attention and a more proactive approach in this field is absolutely necessary. This need has been recognised by Regulatory Authorities and paediatric pharmacovigilance guidelines are currently under preparation. Special emphasis will be given to a review of the existing pharmacovigilance tools and efforts will be put on developing specific tools. As a first step, an inventory of all existing sources of data collection available at EU level in the field of paediatric pharmacovigilance will be undertaken. Another area which requires particular attention relates to the methodologies, and the need to adapt existing or develop new methods.

A class of medicines which will require further work relates to the area of vaccines. Vaccines already differ from other medicines due to their potential for use, on a prophylactic basis in large healthy populations. In view of this there is a need for large studies to evaluate the safety and efficacy of vaccines. A close collaboration with the European Centre for Disease Prevention and Control (ECDC) will be necessary to develop appropriate methods and processes for the conduct of high-quality post-authorisation studies.

III.3 Further Strengthening of the EU Pharmacovigilance System

Initiatives such as the EMEA Road Map to 2010 project and the development of an HMA Strategy on the Future Medicines Regulatory Network aim for a further strengthening of the EU Regulatory System, leading to the establishment of a network of excellence at EU level. The EU Pharmacovigilance System, to which all Competent Authorities (both the NCAs and the EMEA) contribute, is an important pillar of such Regulatory System. The development of a network of excellence provides the best guarantees to EU citizens as regards the promotion and protection of public health.

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Paramount in meeting the ultimate objective of establishing a network of excellence will be to optimise the utilisation of scarce resources and to enhance the overall quality of the EU Regulatory System.

Optimising the Utilisation of Scarce Resources

The high-level surveys of EU pharmacovigilance resources, conducted in 2002 and 2004, indicated the need to make a more efficient use of available resources and expertise. As a result the concept of collaborative working was promoted and in first instance applied to the area of PSUR assessment. Building on this positive experience, further fields of work-sharing will be explored. Making best use of the strengths across the EU in terms of resources and expertise through a more collaborative approach will enable to avoid an unnecessary duplication of work and to free-up scarce resources for other important activities to be performed with a view to strengthening the monitoring of medicines.

Enhancing the Overall Quality of the EU Regulatory System

In order to successfully deal with the rapid pace of change in pharmacovigilance, including challenges stemming from the introduction of emerging therapies and other developments in the area of science, a further increase in the quality of the regulatory activities throughout the EU, in addition to the collaborative approach, will be necessary.

Initiatives which will be undertaken in this field have already been elaborated upon in the EMEA Road Map to 2010 and will relate to the availability of top quality scientific expertise at EU level for the scientific assessment of medicines irrespective of the licensing route, and the availability across the EU of an adequate Quality Assurance System, whereby the principles of good governance, good regulatory practice and integrated quality management will apply to all Competent Authorities.

The availability at EU level of top quality scientific expertise will necessitate:

(1) a strengthening of the competence development at EU level through the establishment of an EU Competence Development Strategy in order to optimise the EU training activities, with particular emphasis on the development of adequate training programmes to further increase the scientific knowledge of experts involved in the review of safety information,
(2) the establishment of an EU-wide up-to-date inventory of all scientific expertise available at NCA level, including expertise coming from academia and learned societies, which will constitute a reliable source of information for all Competent Authorities and encourage the use of the best expertise available in the EU, and
(3) adequate workload and resources planning at EU level, since only effective planning of workload and adequate allocation of resources (whereby collaborative initiatives are an important success factor) can successfully address difficulties encountered in the system, e.g. as regards the operation of the national pharmacovigilance systems.

In order to arrive at an adequate Quality Assurance System the following will be needed:

(1) the introduction of a culture of benchmarking at EU level, across all Regulatory Authorities,
(2) the strengthening of existing peer review systems for the scientific assessment work undertaken, and
(3) the introduction of further organisational and operational improvements, building on initiatives already undertaken such as the revised PhVWP mandate.

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IV Next Steps

As already indicated, a number of environmental changes (strategic developments, legislative initiatives and emerging safety issues for high-profile medicines) have resulted in complementary initiatives, not included in the initial ERMS as published in January 2003. As a consequence, HMA and the EMEA will undertake a revision of the 2003 ERMS.

Furthermore, the EMEA and HMA will continuously monitor the further implementation of the ERMS. Such monitoring will be translated in a yearly status report which will be jointly published by the EMEA and HMA. Where considered appropriate, additional initiatives will be undertaken to meet the ultimate objective of achieving high standards of public health protection for all medicines available on the EU market.

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