

*ESTABLISHING A EUROPEAN RISK  
MANAGEMENT STRATEGY*

*SUMMARY REPORT OF THE HEADS OF AGENCIES  
AD HOC WORKING GROUP*

**Based on the full report adopted by the**

**HoA**  
Heads of Agencies

**January 2003**

# HEADS OF AGENCIES WORKING GROUP REPORT

## ESTABLISHING A EUROPEAN RISK MANAGEMENT STRATEGY

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# **ESTABLISHING A EUROPEAN RISK MANAGEMENT STRATEGY**

## **Executive Summary**

### **Introduction**

1. European systems for monitoring the safety of medicines in clinical use and taking action to minimise risk have come under scrutiny, particularly following a high profile drug withdrawal in 2001. The high level G10 initiative has made recommendations (1) and in May 2002 the European Agency for the evaluation of Medicines Products (EMA) presented proposals for the establishment of a risk management strategy concentrating on centrally authorised products and referrals (2). Welcoming this initiative, the Heads of Agencies wished to take stock of the current status of European pharmacovigilance for all medicinal products, and to explore how the conduct of pharmacovigilance could be strengthened.
2. In July 2002 Heads of Agencies agreed a mandate for an ad hoc Working Group comprising participants from Denmark, France, Germany, Spain, UK and EMA. The Group adopted the following remit:

To develop a European Strategy for Risk Management which: -

- Builds on Competent Authorities (CAs) resources and expertise and incorporates the EMA's role in the co-ordination of the supervision of products authorised in the Community
- Supports consistent, robust decision making
- Ensures accessible information on safety, including information exchange between CAs
- Reduces reduplication of work
- Is demonstrably effective in protecting public health.

### **Rationale and Justification for a European Strategy**

3. A review of the lessons learnt in Europe from experience in managing drug safety issues was conducted. Based on casework history rather than on objective outcome measures, its extent and diversity nonetheless fully justified the preparation of a coherent European Risk Management Strategy. The process of bringing together examples of lessons learnt also illustrated the need for core performance standards, an effective issues tracking and management system, and agreed methodologies for audit and monitoring outcomes.

### **Role of the National Competent Authorities**

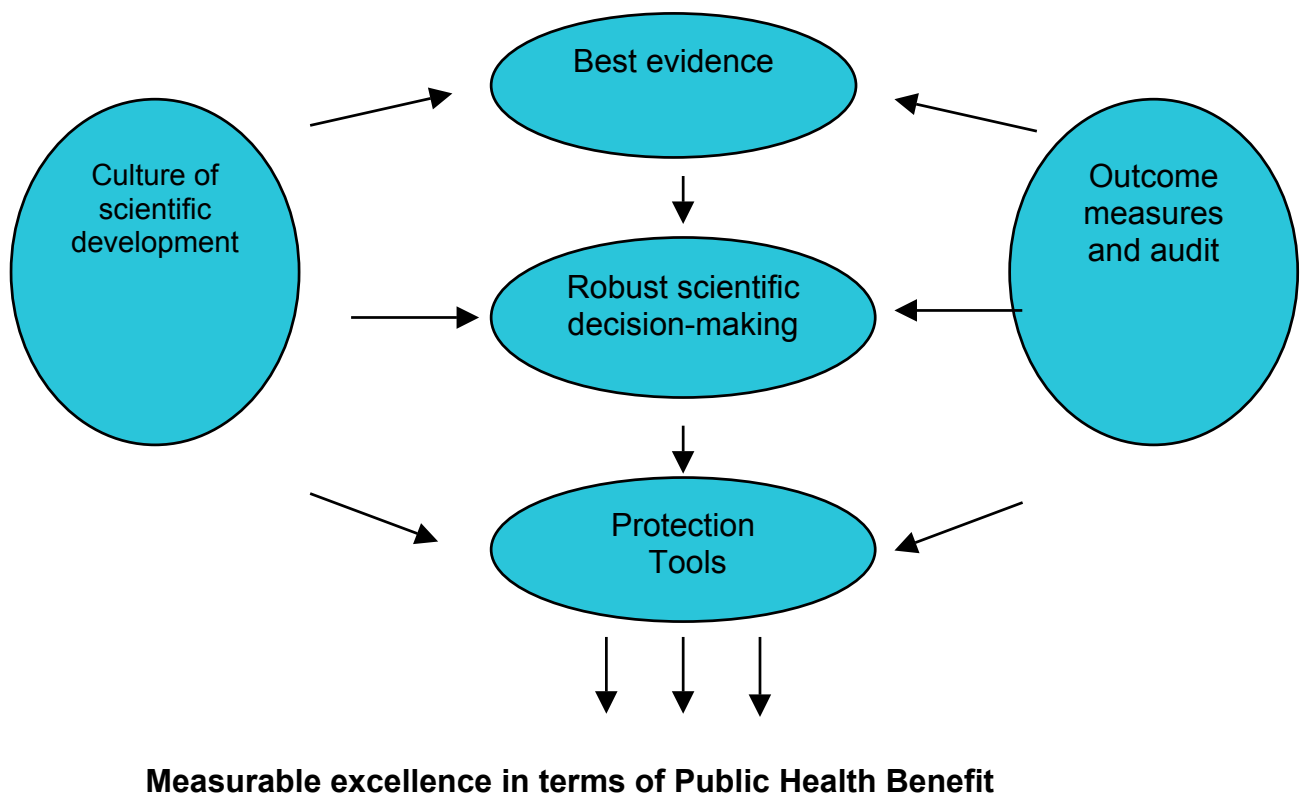
4. The role played by each national competent authority in pharmacovigilance is vitally important to the effectiveness of the European systems as a whole, including the core activities set out in Notice to Applicants Volume IX: EU Pharmacovigilance Rules for Human and Veterinary Medicinal Products:

- Collect and analyse Adverse Drug Reaction (ADR) data from national health care professionals, providing feedback and interaction to encourage reporting
- Communicate ADR reports to industry and via Eudravigilance to the EMEA
- Assess Periodic Safety Update Reports (PSURs) and post authorisation safety studies for nationally authorised products, Centrally Authorised Products (CAPs) and Mutual Recognition (MR) products
- Perform signal detection and risk assessment for nationally authorised products, CAPs and MR products
- Communicate safety information to health care professionals and the public
- Undertake compliance measures to ensure legal requirements are met
- Educate relevant stakeholders in pharmacovigilance
- Implement Community decisions impacting on nationally authorised products.

There is diversity across Europe in the resource, expertise and systems for conducting these functions and activities. In order to build on strengths, it will be important to have a comprehensive picture of these assets and a survey is proposed to develop this.

### Evidence base for pharmacovigilance

5. A recently developed model for excellence in pharmacovigilance provides a basis for structured discussion (3).



Access to “Best Evidence” is fundamental to strengthening pharmacovigilance and the limitations of current data requires action. Such action needs to include a move up the “evidence hierarchy” e.g. via better utilisation of databases for epidemiological studies (such as the General Practice Research Database in UK and similar under development in Spain) and systematic collection of drug utilisation data. There are also opportunities for reducing duplication of work.

### **Achieving robust decision making**

6. Current decision making processes do not uniformly deliver timely outputs, implemented in all MS. In particular, the Pharmacovigilance Working Party (PhVWP) occupies a central role in the EU system and its operation needs to be reviewed and re-focussed. The current discussions on the future role of Mutual Recognition Facilitation Group (MRFG) taking place in the 2001 Review offer an important opportunity. The MRFG will become a Co-ordinating Group whose future role is currently under consideration. It is also timely to make proposals on the future role of the PhVWP.

### **Pharmacovigilance tools including communications**

7. The increasing reliance in decision making on the capability of Marketing Authorisation Holders (MAHs) and CAs to agree and implement risk management plans leads to a requirement for agreed guidance in this area. Proposals to set the template for risk management plans need to be taken forward. Effective communications between CAs are key to timely action on safety issues and to the successful implementation of regulatory action.

### **Conclusions**

8. The Working Group set out to produce a strategy which would be capable of achieving high standards of public health protection for all medicines, regardless of route of authorisation, which would further develop the collaborative approach to maximise use of resources available within the Community, recognising that all Competent Authorities have a role to play. Each element of the strategy is underpinned by these aims.

### **Proposals to build a European Risk Management Strategy**

9. Heads of Agencies agreed the following five components of a European strategy
  - Undertake a pharmacovigilance resource survey across the CAs, to enable future planning to optimise utilisation of resource and expertise, and encourage collaborative working
  - Review the role and responsibilities of the Pharmacovigilance Working Party in collaboration with the EMEA/CPMP and develop the role of the new Co-ordinating Body, to improve decision-making

- Explore current communication tools and mechanisms in order to develop an effective pharmacovigilance information management tool
  - Develop a European strategy to both make better use of the existing sources of evidence for pharmacovigilance and to enhance it
  - Develop guidance on risk management plans and put in place mechanisms for outcome measures and audit.
10. Finally, Heads of Agencies recognised that building a European strategy is a major undertaking which would require prioritisation of short, medium and long term objectives, and decisions on how and by whom the work should be taken forward.

## References

1. G10 Medicines Report. Report of the High Level Group on Innovation and Provision of Medicines in the European Union – 7 May 2002 © European Communities.
2. Proposals for the establishment of an EMEA Risk Management strategy, concentrating on Centrally Authorised Products and Referrals (Doc.Ref EMEA/16720/02/Rev 2) 9 July 2002.
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## **CHAPTER ONE**

### **Rationale and justification**

#### **Purpose of chapter**

1. To consider the justification for a European risk management strategy based on a distributed, collaborative approach. The chapter is designed to set the scene, to identify drivers for change as well as the lessons to be learned – with relevant examples, from recent experience of handling drug safety issues.

#### **Background**

2. The legal framework for pharmacovigilance in the Community is set out in European Law, codified in Directive 2001/83 EEC and in Regulation 2309/93. The Directive requires the Competent Authorities of the Member States to undertake certain actions to deliver pharmacovigilance in their territory. This reflects the fact that the majority of Marketing Authorisations in the Community are, and will continue to be for some years, national authorisations, for which the Member States have legal responsibility.

#### **Future perspective**

3. The EMEA's proposed Risk Management Strategy and the 2001 Review legislative proposals offer the opportunity to move towards a more centralised model of pharmacovigilance. The Heads of Agencies recognised the need to evaluate the extent to which such changes would impact on the ability of the Competent Authorities to fulfil their responsibilities for public health and in the light of this, develop a strategy and vision to determine the extent and pace of change.

#### **What is the need for a European Strategy?**

4. Pharmacovigilance is a vital preventive public health function which must be capable of detecting and rapidly responding to safety hazards anywhere in the EU. It is increasingly important with the growing emphasis on making new medicines, tested in small numbers of patients, available at an early stage, and shifts the balance of regulatory control towards post authorisation risk management. A European strategy is needed to promote safe use of medicines and prevent adverse drug reactions thereby protecting public health, and this can best be achieved by using co-ordinated pan-European systems. There is also common agreement that pharmacovigilance activities should be reinforced for all medicinal products, regardless of the authorisation procedure. Other drivers for action include the globalisation of pharmacovigilance issues; pressure from industry for a consistent approach between EU regulators and the increasing workload in pharmacovigilance. Making best use of the distributed, collaborative system offers advantages to public health:-

- **Resources for pharmacovigilance** are distributed and limited. Their organisation and delivery is based on mechanisms in place within the Member States and they have developed in such a way as to be integral to the role of the national Competent Authority. Such a distributed system can be used flexibly to take account of “demand” locally.
- **Common approaches** to managing drug safety issues making the best use of the regulatory options available in the Community system to ensure a harmonised way of working, yet with sufficient flexibility to take account of local needs.
- **Enlargement of the EU** presents imminent challenges to the operation of all the systems of the Community, not least medicines regulation. Making the best use of increased resource in drug regulation offers opportunities which must be developed.
- **Cultural and healthcare delivery differences** mean that the flexibilities offered by a distributed system can take account of local circumstances to produce speedy action to protect public health.
- **Local communications** can play an important part in pharmacovigilance, both in enabling the exchange of less formal information (between health care professionals, authorities, Marketing Authorisation Holders and the public), and in relation to risk communication. Mechanisms for enforcement, feedback and follow up are also delivered at a local level.
- **Rapid pace of change in pharmacovigilance**, including the need to embrace new science and technologies suggests that a collaborative approach would make the best use of limited resources.

### **Strengths and weaknesses, lessons to be learnt**

5. In view of the drivers for change, there is a need to identify the strengths and weaknesses of the current EU pharmacovigilance system. This provides an opportunity to build on the strengths and focus on solutions for areas of weakness. Using the pharmacovigilance ‘excellence model’ as a template, key areas include: best evidence, robust decision making, tools to protect public health, outcome measures and audit.

#### **5.1 Best evidence**

##### *a) Data collection:*

A devolved system based on Member States is ideally placed to collect information (including single case reports) from healthcare professionals and possibly users of medicines and is also ideally organised to provide reporters with feedback. The proportion of ADR reporting which comes direct from health care professionals in Europe is much higher than in USA.

On the other hand, the capability of different MSs to collect data is variable and there is concern about non-compliance by MA holders with pharmacovigilance obligations. There are examples where Competent Authorities may not have received key data in a timely manner and there is a need to strengthen their monitoring/enforcing role.

b) *Data management:*

There are important strengths in data management in Europe. The EU has led the world in terms of management of single case reports. This leadership role should be maintained and extended to management of other data types e.g. electronic submission of PSURs and study reports. Eudravigilance, once fully populated, will facilitate the conduct of pharmacovigilance at an EU level as a tool for data collection and analysis.

c) *Signal detection:*

The EU has led the world in the application of statistical methods to detecting safety signals from spontaneous data e.g. the routine use of Proportional Reporting Ratios (PRRs). These methods have identified safety signals at an earlier stage than might otherwise have occurred but there is no common methodology.

The devolved system allows detection of local safety issues and also ensures that multiple groups are performing signal detection in parallel (maximising the chances of detection). This may be particularly useful in relation to changes in the profile of known ADRs. However, there may be duplication of effort and consequent poor use of finite pharmacovigilance resource. Currently there is a lack of timely access for all Competent Authorities to all relevant data.

## 5.2 **Robust decision making**

a) *Risk assessment and quantification:*

There are risk assessment teams available in all the Competent Authorities, however work could be better shared (particularly for nationally authorised products). One weakness is difficulty prioritising safety issues at an EU level. Priority may be different for different Competent Authorities. There is finite assessor resource across the EU and varying levels of training and experience. New therapies where specialised expertise is required also pose a challenge. A further issue is that many Member States lack drug utilisation data.

b) *Benefit risk evaluation and decision making*

Current EU referral systems are capable of supporting high quality benefit:risk assessments on major pharmacovigilance issues. However, due to the time and assessor resource required, such assessments need to be reserved for key public health issues. The EU has the expertise (based in the Member States) to make sound decisions on major pharmacovigilance issues. However, identifying and securing this resource requires thought and planning. Each issue requires specific expertise and there is a need for greater utilisation of ad-hoc expert groups as was recently set up on Hormone Replacement Therapy. The current devolved system is ideally

organised for peer review of assessments and decisions. This increases the quality of the system.

Weaknesses include long timescales for formal referrals and consequent delay of definitive public health protection measures. The scope of the assessment could often be more focussed. This would allow more assessments to be conducted at an EU level and issues to be resolved more quickly. Furthermore, criteria for making EU referrals have not been laid down explicitly, nor is there standardised interpretation of “in the interests of the Community”. Assessments do not consistently follow relevant guidelines on the conduct of benefit risk assessment particularly in terms of consistent ‘options analysis’. Decision-making could be improved by more consistent structuring of assessments and systematic presentation of the regulatory options with the potential implications of each discussed.

### 5.3 **Tools to protect public health**

#### *Regulatory action and implementation*

Referrals to the CPMP have been effective in leading to harmonised regulatory action across Europe which has a clear legal basis. But different authorisation types pose a challenge for reviews of groups of medicines in the same class as different committees may be responsible (unless an article 31 referral is made to the CPMP).

The PhVWP has evolved over the past decade to become a forum for information exchange and consensus building between the Member States. Its increasing workload and variety of tasks and deliverables suggest that its remit and outputs require review and streamlining. Furthermore, opinions from the PhVWP are not binding and depend on individual Competent Authorities to negotiate with individual companies. Examples include the CPMP conclusions on Combined Oral Contraceptives (COCs) and VTE and the PhVWP class review of statins and muscular toxicity.

Implementing changes to the Summary of Product Characteristics can be slow using the current type II variation procedure (especially for centrally authorised products) and the Urgent Safety Restriction procedure can be difficult to operate. The proposed changes to the Variation Regulation should provide more appropriate procedural options. Finally, legal hurdles in some Member States make risk minimisation strategies including registries, restricted distribution, patient consent etc, difficult to implement at an EU-wide level. Further work is required to define a framework at a national level for implementing EU-wide risk minimisation plans.

#### *Communication*

The Rapid Alert and Infobox systems work well but further improvements could be made. An EU-wide pharmacovigilance information tracking and management system would be a fundamentally important step towards strengthening the system.

A devolved system is ideal for reaching the target audience, including health care professionals and patients and meeting their needs. Information distribution systems vary, however, in different Member States and this may have an impact when co-ordinating communications to stakeholders. For example, the communication exercise on the Combined Oral Contraceptives and venous thromboembolism issue was limited by the distribution networks in some Member States (i.e. communicating at the rate of the slowest distribution system). There is a lack of expertise on risk communication at an EU level. Furthermore, experience of managing the media is relatively limited. Early warning of action at a national level, including the sharing of press briefing and question and answer material, could be improved.

#### **5.4 Audit and outcome measures**

Work has started on common standards for Good Vigilance Practice (GVP) for regulators, but progress has so far been slow. Standards for GVP will also be particularly important as the EU undergoes enlargement. Setting standards is a prerequisite to introducing regular audit of the EU pharmacovigilance systems. Work has started within the PhVWP on the introduction of outcome measures following regulatory action i.e. assessing whether action taken effectively protected public health. This work needs to be consolidated.

### **Conclusions**

6. There is a clear justification from the strengths and weaknesses identified for the development of a European Risk Management Strategy. Recent examples of European risk management issues have been considered and represent a strong base for the development of the strategy.

## CHAPTER TWO

### Responsibilities of the National Competent Authorities (NCAs)

#### Purpose of chapter

1. This chapter focuses on the responsibilities of the National Competent Authorities, listing the most important issues in this respect, and highlighting particular areas for improvement.

#### Legal framework

2. The legal framework for pharmacovigilance in the Community is set out in European Law, codified in Directive 2001/83 EEC. The Directive requires the Competent Authorities of the Member States to undertake certain actions within their national territory. Based on this Directive, the Notice To Applicants Volume IX: EU Pharmacovigilance Rules for Human and Veterinary Medicinal Products(1), outlines these responsibilities in detail. In addition there are national procedures for products authorised nationally.

### Responsibilities of the National Competent Authorities in pharmacovigilance

3. The National Competent Authorities should provide

#### EU-level

- Delegates for the CPMP and PhVWP
- Scientific assessments of PSURs for medicinal products for which the NCAs are rapporteur/co-rapporteur or reference member state, and other post-authorisation commitments
- Scientific advice in case of safety issues for centrally authorised medicinal products for which the NCA is rapporteur/co-rapporteur
- Request information via / respond to Non Urgent Infofaxes and Rapid Alerts
- Provide necessary equipment and fulfil obligations regarding the Eudravigilance system
- Act as rapporteur for referrals

#### National level

- Collect, analyse and register ADR data collected spontaneously from national Health Care Professionals
- Perform national signal generation
- Forward ADR reports via the Eudravigilance system to the EMEA
- Forward ADR reports to industry
- Assess PSURs for nationally authorised medicinal products
- Inform relevant parties of important new safety information and initiatives
- Educate relevant parties in pharmacovigilance
- Enforce compliance by MAHs.

## Current weaknesses / areas of concern and proposals for improvement

4. The PhWVP has, on several occasions, discussed the principles of Good Vigilance Practice(2). The following issues relating to the responsibilities of the NCAs have been addressed:

4.1 Involvement of pharmacovigilance experts in the pre-registration phase

The NCAs (and EU competent agencies) need to work more proactively, such that there is the participation of pharmacovigilance expertise in safety assessments before and at time of approval in order to plan for necessary and relevant postmarketing surveillance activities.

4.2 Collaboration in the pre-registration and post-authorisation phases

CAs must ensure there is an optimal collaboration between different units within the agency. There are barriers and obstacles at the national level with regard to the co-operation between pre- and post-registration units and staff e.g. the initiation of variation procedures following recommendations from the PhVWP; insufficient sharing of information between CPMP and PhVWP delegates.

4.3 Additional experts

NCAs should provide additional experts for the evaluation of safety data as appropriate. The EMEA paper on a Risk Management Strategy for centrally authorised products and referrals (3) proposed a need for experts in the areas of pharmacovigilance, clinical pharmacology, pharmacoepidemiology and communication, with these experts preferably to be nominated by the MSs. The PhVWP considered it essential that these experts from the MSs could also provide support to PhV work via the NCAs.

4.4 Data collection

NCAs should continuously try to improve the frequency and quality of spontaneous ADR reports and should explore alternative ways of data collection (e.g. registries, co-operation with academia)

4.5 Signal generation utilising the EU database

With the establishment of a common EU database for ADRs from all MSs there is a need for determining the responsibility for signal generation, e.g. the responsibility of the diverse NCAs.

4.6 Collaboration with Academia / Universities

This has two purposes; education and development of staff and application of scientific methods in providing and analysing drug safety information (including “moving up the evidence hierarchy”).

4.7 Audit.

NCAs should perform audit and monitor outcomes of activities, thereby being able to strengthen pharmacovigilance procedures and improve safety.

## Conclusions and proposals

5. The basis for strong European pharmacovigilance systems is the sum of the capability and contribution of individual Member States. The responsibilities of NCAs have been pointed out, together with areas of concern and proposals for improvement. The role of the NCAs in improving risk detection, risk assessment, risk communication and risk minimisation should be further explored, in particular with a view to greater collaboration and improved communication with less duplication of work. There is diversity across Europe in the resources, expertise and systems for conducting these functions and activities. In order to build on strengths, it will be important to develop a comprehensive picture of these assets and a survey is proposed.
  
1. Notice To Applicants Volume 9: EU Pharmacovigilance Rules for Human and Veterinary Medicinal Products [.http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm](http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm)
2. Pharmacovigilance Working Party “Working Document” dated 25 September 2002 “General Pharmacovigilance and Organisational Issues” - provides the viewpoint of the PhVWP and has not been considered by CPMP. The draft does not necessarily represent the views of the EMEA or of the Member States.
3. Proposals for the establishment of an EMEA Risk Management strategy, concentrating on Centrally Authorised Products and Referrals (Doc.Ref EMEA/16720/02/Rev 2) 9 July 2002.

## **CHAPTER THREE**

### **Best evidence in pharmacovigilance**

#### **Purpose of chapter**

1. For several decades spontaneous reports of suspected adverse drug reactions received from health care professionals have been the cornerstone of drug surveillance, and they are still an important part of the evidence and documentation used in the assessment of drug safety. There is, however, a need for improving drug safety surveillance by introducing new tools and scientific methodologies (moving up the “evidential hierarchy”) to reach more scientifically reliable data supportive of regulatory decisions.
2. This chapter outlines the limitations of the current evidence base of pharmacovigilance as well as proposals for improvement. The key areas for consideration are data collection and management, and risk quantification and assessment.

#### **Spontaneous reporting**

3. Spontaneous ADR reporting is the main source of information for detection of signals of drug safety hazard and should remain one of the cornerstones of a comprehensive safety monitoring programme. Permanent programs should be promoted, encouraging health professionals to report. The choice of methods should be made at the national level, as their success is partly dependent on the cultural environment. Some methods to encourage reporting are:
  - feed-back information and dialogue with reporters
  - linkage of the reporting to a service delivered to reporters; this service may take the form of a literature review on the same adverse drug reaction or on adverse reactions associated with the suspected drug
  - establishment of procedures for facilitating reporting (i.e. electronic forms).
4. Up to now, much emphasis has been placed on the reporting from general practitioners and, lately, by pharmacists. Given the increasing number of products for hospital use and/or prescription restricted to certain specialists, and that a number of serious reactions require hospitalisation, it is important that spontaneous reporting in the hospital setting should be stimulated.
5. The Eudravigilance database and data processing network should facilitate the exchange of Individual Case Safety Reports (ICSRs) and the integration of automated tools of signal detection.
6. Compliance of Marketing Authorisation Holders with their reporting obligations should be monitored, performing inspections of MA holders’ pharmacovigilance systems when deemed necessary.

## **Periodic Safety Update Reports**

7. Periodic Safety Update Reports (PSURs) are a major source of aggregated safety information, analysed and interpreted and set in a global regulatory context. It is probably under-utilised at present due to a number of factors. Efforts should be made to optimise the management and assessment of PSURs, avoiding duplication of work, especially with regard to nationally authorised products.

## **Registries and follow-up programs**

8. For certain safety issues, certain medicinal products, or certain populations, spontaneous reporting may not be sensitive enough and needs to be complemented with other permanent sources of information. Registries may address specific diseases frequently associated with drugs (e.g. haematological dyscrasias, severe hepatic and skin disorders, congenital malformations). Follow-up programs, which may concern certain populations (e.g. pregnant women, HIV patients), or populations exposed to special medicinal products (e.g. biologicals, xenogeneic cellular products), constitute another potential source of information to be developed.
9. Follow up programs are particularly relevant for novel drugs that are designed to work through new biological principles since they may give rise to serious and unpredictable adverse reactions that can be detected only after the drug has been used by a sufficient number of patients for a sufficiently long time. There is an obvious need to obtain as quickly as possible adequate information to define the safe and rational use of the new drug.
10. As agencies by themselves do not normally have the capability to set up such registries or follow-up programs, the most effective way to proceed is to formalise co-operative agreements with professionals from academia, hospital settings or scientific societies who may run such registries or programs. This will assure the prompt transmission of important information, and the use of the registry or program not only for signal amplification but also in some instances for hypothesis-testing and a first-hand evaluation of the problem observed.
11. An enquiry all over the European Union to ascertain the existing registries or follow-up programs would be the first step to be taken. Competent authorities should encourage co-ordination of registries/programs to participate in initiatives for setting up European networks, enhancing in this way the capability for risk generation/quantification. Guarantees for continuous and adequate funding are essential for the success of such initiatives.

## **Risk quantification and risk assessment**

12. On frequent occasions, risk assessment and regulatory decisions are mainly based on spontaneous reporting whose limitations are well-known (e.g. under-reporting, risk of bias, unsuitable for calculation of frequencies etc). For regulators it is unsatisfactory to base judgements and take actions with a substantial degree of uncertainty and without any accurate measurement of the magnitude of the risk and its impact on public health (risk quantification).
13. Risk quantification normally requires formal epidemiologic studies to be performed, in order to provide valid and precise measures of frequency and association. However, this is difficult if not impossible to be done within the timeframe of pharmacovigilance unless efficient and validated data sources exist. Automated healthcare databases based on a linkage of both prescription data and clinical information are probably the best approach and should be developed in different Member States or, if they already exist, validated for pharmacoepidemiologic purposes.
14. Although there are a number of good databases in the European Union, they are still scarce. Multi-site database studies will be needed for the early postmarketing phase, when even large databases like the UK's General Practice Research Data (GPRD) are underpowered. National agencies must support (or lead) such important developments. Formal agreements with the institutions running the databases (e.g. GPRD, IMS) in order to assure access to the raw data, and/or with the epidemiologic teams with experience in conducting studies using such databases, will be essential in the near future.

## **Drug utilisation data**

15. For an adequate risk assessment, it is important to have knowledge about the extent of the population exposed and drug utilisation patterns, including prescribed daily doses, treatment duration, therapeutic indications and co-medications. Consideration should be given to a more extensive use of prescription databases for this purpose. Attempts should be made to establish links across European countries in order to obtain a global view of drug utilisation patterns in Europe.

## **Post authorisation safety studies**

16. Due to the need for intensified early post-marketing surveillance and, whenever possible, accurate estimates of risk magnitude, it is increasingly common that certain commitments are agreed with the Marketing Authorisation Holder (MAH) at the time of granting the marketing authorisation. Through them, MAHs commit themselves to perform safety studies (e.g. risk estimation, identification of population at risk). It is general experience that protocols submitted by the MAH are often of poor quality and it takes a very long time to reach agreement on the final protocols. The timetable, study questions to be answered and study protocols should be endorsed by PhVWP and CPMP before authorisation is granted.

## **Summary of proposed actions to be taken for enhancing best evidence**

17. In conclusion, in order to strengthen pharmacovigilance, establishing a framework for moving to 'best evidence' is of prime importance. This will include the following:
- To establish mechanisms and procedures for stimulating spontaneous reporting from health professionals, especially in hospital settings
  - To collaborate in designing and applying tools to support signal generation
  - To minimise work duplication in the management of PSURs
  - To promote the development and maintenance of registries and follow-up programs collaborating with academia, scientific societies and hospitals.
  - To promote and contribute to the creation of adequate and permanent automated data sources for the performance of pharmacoepidemiologic studies
  - At the time of granting marketing authorisation, to agree safety study protocols to be performed
  - National Competent Authorities and pharmaceutical companies to implement the electronic reporting of Individual Case Safety Reports through the EudraVigilance database and data-processing network.

## CHAPTER FOUR

### Achieving robust decision making

#### Purpose of chapter

1. The purpose of this chapter is to set out the issues concerning the risk management decision making process and the links to implementation of recommendations and decisions made within the Mutual Recognition Facilitation Group (MRFG) and the Pharmacovigilance Working Party (PhVWP).

#### Background

2. There is an increasing number of referrals to CPMP and a proposed move towards a more centralised model of decision making, using experts to facilitate CPMP. This raises questions of i) accountability and ii) the capacity of Community systems and procedures to be able to manage the volume of data and decision making. There are currently obstacles to the implementation of recommendations from PhVWP and consistent agreed procedures are needed for their national implementation. The variable timescales for implementation of safety recommendations within Member States is an issue of particular concern.
3. In terms of volume of work, there are currently approximately 600 mutual recognition procedures completed and this number will continue to increase. The majority of marketing authorisations within Member States are national and will continue to be for the next decade. However, pharmacovigilance issues are increasingly being considered at a European level, and as referrals to CPMP are made, more products subsequently enter the mutual recognition process. The issue of overload in any one system is an important consideration as it will impact on the capability for timely action on safety issues.

#### Pharmacovigilance Working Party - evolving role

4. The existing mandate of the Pharmacovigilance Working Party was agreed in 1995 and has not been reviewed since then. Its purpose is to provide a forum for dialogue and understanding between the MSs and EMEA on pharmacovigilance within a framework with three main components:
  - i) Organisational matters:
    - Developing common principles and procedures for detecting signals, assessment, sharing information and communication.
    - Preparing and revising guidelines
    - Be focus and catalyst for training, methodology, IT, and international activities.

- ii) Product related issues at CPMP's request with a precise mandate and in a defined timeframe, recommending options to CPMP.
- iii) Other inquiries at the request of National Authorities: review of signals and evaluation of issues on an informal basis, communicated to CPMP for information only.

The membership comprises one delegate per Member State, an observer from the European Commission, ad hoc expertise as requested and Secretariat provided by EMEA.

### **Achievements of PhVWP**

5. Since its start the PhVWP has become an effective forum for the exchange of information between its members, for reaching consensus on difficult safety issues facing the community and the development of procedures and guidelines. Furthermore, the PhVWP has had some notable successes, e.g:
  - Major guidelines written and updated e.g. Volume IX of Notice to Applicants
  - Input on multidisciplinary topics e.g. European SPC guideline
  - Setting international standards e.g. MedDRA
  - Effectively resolving safety issues, both urgent issues e.g. HRT, and large safety reviews e.g. statins and muscle toxicity.

### **Challenges facing PhVWP**

6. Despite its successful track record, the PhVWP faces new and evolving challenges. These include:
  - Expansion of the EU with up to 25 Member States
  - Increasing work-load
  - Complex “reporting lines” for centrally authorised, MR and nationally authorised products
  - Nature of the work changing, e.g. need to consider post-authorisation safety study protocols, pharmacovigilance specifications and plans, MAH compliance, process and outcome audit.
7. Some challenges may limit the effectiveness of the PhVWP in the future unless they are dealt with, particularly
  - Implementation of PhVWP recommendations for MR and nationally authorised products
  - Communication on such issues.

### **Process for Decision Making and Implementation**

8. The PhVWP evaluates issues relating to national and MR products, usually reaching a consensus on required regulatory action, which is then taken forward at national level or through the MR process as appropriate. Implementation by

Member States of recommendations of PhVWP in relation to national MAs has proved difficult.

9. The variations procedures available or about to become available are:
- Urgent Safety Restrictions – decision taken within 24 hours and followed up with a formal Type II variation procedure.
  - Type II variations – a 90-day procedure with the possibility for a clock stop.
  - New variation procedure for routine safety updates - the Notice to Applicants Working Group are in the final stages of work to introduce changes to the Variation Regulations. These will introduce a rapid procedure for routine safety variations requiring changes to the SPC. A maximum time frame of 30 days is to be introduced compared to the current 90-day procedure. The MRFG has also prepared a series of Best Practice guidance to assist its implementation. There should be prompt resolution of issues and implementation of the Variation Regulation amendments to assist timely approval of safety variations.

#### **Referrals to CPMP through Articles 29, 30, 31 and 35**

10. Many successful safety variations have been concluded through the current mutual recognition variation system with no need for a CPMP referral. When agreement can not be reached by Member States or where the interests of the Community are involved, the matter may be referred to the CPMP. This will result in a Commission decision that is binding in all Member States and has to be implemented within a set timescale. The Article 31 provision has wide implications as the decision applies to all the relevant products authorised in the EU and these national products now become subject to MR procedures with continued maintenance of the harmonisation. The question is whether the term “interests of the Community” needs better definition (referrals may have been used for political rather than community public health reasons) for example where there are particularly complex or significant decisions.
11. Voluntary agreements are in place with industry representatives to ensure that generic products are harmonised in line with Article 30 originator referrals. If harmonisation cannot be maintained through voluntary agreements, formal referral processes may need to be initiated.

#### **Periodic Safety Update Reports**

12. Current systems for processing PSURs result in enormous duplication of effort amongst Member States. Processes are in place to ensure co-ordination of work associated with PSURs for products within MR but there is potential for much improvement in the process. Appropriate use of PSURs is a powerful tool in risk assessment and this is an area that would merit attention, particularly in view of their increased importance foreseen in the 2001 Review proposals (PSURs every 3 years).

## Use of expert groups

13. Ad hoc expert groups can be seen as an important model for using expertise and reaching consensus without the need for CPMP referral. The MRFG expert sub-group for the HRT core SPC has shown such a model to be successful in practice. This MRFG sub-group used the expertise of PhVWP to agree a core SPC for HRT products that will form the basis for future MR procedures. When new data became available, the group was quickly reconvened and an updated position reached. Member states are able to use the agreed European scientific and regulatory position as a basis for national implementation thus assisting both horizontal and vertical harmonisation across member states. No CPMP referral was necessary.

## Review of Pharmacovigilance Working Party role

14. In reviewing the role and remit of PhVWP, there are two key areas for consideration – the scope and organisation of work, and the membership and expertise needed. The status of PhVWP recommendations also needs to be clarified and communication options considered. Finally logistic support, its structure and funding need to be considered. This parallels the considerations currently in hand in the 2001 Review for MRFG.
15. Three options for how a review might be taken forward could be:
  - i) Refine and clarify key responsibilities, providing for clear deadlines and outputs
  - ii) Remove or minimise work with less immediate public health impact – no longer perform or remit to another body
  - iii) Take on new responsibilities.
- i) Key responsibilities of the PhVWP would be:
  - Review of potential signals providing advice on confirmation and quantification of risk
  - Review risk and preferably risk:benefit assessments (including referrals) advising CPMP/MRFG on regulatory options
  - Advice on risk management pre and post authorisation
  - Promote communication and exchange of information between Member States and EMEA
- ii) Areas to be minimised/remitted to other bodies could include :
  - Class reviews
  - IT development
  - Training in pharmacovigilance assessment
  - Revision of guidelines e.g. NTA.
- iii) New responsibilities could include:
  - Communication of PhVWP advice
  - Monitoring outcome and audit.

## **New Co-ordination Group to replace MRFG**

16. The 2001 Review introduces the new concept of a Co-ordination Group which is giving a legal basis to the existing informal arrangements for MRFG. The proposed legislation allows for this group to draw up its own Rules of Procedure. An MRFG sub-group has started work on this task. As part of this work the matter of opinions and decisions resulting from the new group is under consideration. A key issue is how to achieve the implementation of the decisions made by the Group on a national level across the EU possibly using Heads of Agencies Group for endorsement and review of progress.

## **Conclusion**

17. In order to maximise opportunity of effective decision making and collaboration on risk management issues, the following are proposed:
  - i) A review of the mandate of the Pharmacovigilance Working Party, in collaboration with the EMEA, considering in particular the options for improving the availability of timely advice on risk assessments and risk management plans.
  - ii) Recommend a risk management model for decision making and implementation of decisions emerging directly from MRFG, and the Co-ordination Group in the future. The future role of the Co-ordination Group and rules of procedure should be defined so as to support this.
  - iii) Request MRFG in liaison with PhVWP to undertake a programme of recommendations for best practice to ensure effective co-ordination of decision making and rapid implementation on risk management issues.
  - iv) Encourage co-operation between MRFG and PhVWP supported by an electronic network for information sharing on risk issues.

## CHAPTER FIVE

### Risk Management Plans

#### Purpose of chapter

1. This chapter provides further background and explanation on current developments in relation to risk management plans as a basis for discussion on the need to develop formal guidance. The key concept is that public health will be better protected by earlier planning of pharmacovigilance and more formalised agreement of risk minimisation strategies.

#### Terminology and definitions

2. The term ‘risk management’ has been used by different stakeholders to mean different things. For the purposes of this paper the following terminology is used:
  - risk management – the identification and implementation of strategies to reduce risk to individuals and populations
  - product risk management plan – a plan identifying the risks associated with a medicinal product, methods to further clarify the safety profile of a product, and ways to minimise risk to individual patients in clinical use. This is made of three elements:

Pharmacovigilance specification – a structured method for documenting the established risks of a drug and the potential for unidentified risks at the time of marketing authorisation

Pharmacovigilance plan – a plan proposing collection of data relevant to the safety profile of a medicinal product once it is marketed and aiming to demonstrate safety as well as identifying harm

Risk minimisation ‘toolkit’ - strategies to reduce risk to individual patients and populations.

#### Background and history

3. Effective pharmacovigilance systems protect public health by reducing the burden of adverse drug reactions. In this context, pharmacovigilance refers to the scientific activities relating to the detection, assessment, understanding and prevention of adverse effect or any other drug related problem.
4. Early planning of pharmacovigilance which is clearly related to what is known about the safety profile of a drug is likely to lead to more effective risk management and therefore more effective protection of public health. Within the EU already there are guidelines on conducting post-authorisation safety studies in Notice To Applicants Volume IX: EU Pharmacovigilance Rules for Human and Veterinary Medicinal Products. However, various stakeholders within Europe

have identified the need to start planning pharmacovigilance much earlier in the life cycle of a drug, ideally before a product gains a marketing authorisation.

5. In 1999 the FDA published a strategy on risk management. In addition, the European Parliament amendments to the Commission's 2001 Review proposals refer to risk management plans.
6. In the UK, work conducted in 2001 – 2002 on a model for “excellence in pharmacovigilance” (see Executive Summary) has also identified the need for better pharmacovigilance planning and many of the concepts coming out of the “excellence in pharmacovigilance” project have been fed into the ICH discussion and are included in this Report.

### **Application of Risk Management Plans**

Risk Management plans would be particularly relevant to:

- new chemical entities and biotech derived products
- orphan medicinal products
- significant changes in established products (e.g new form/route of administration)
- established products introduced to new populations or significant new indications
- established products when reclassified from prescription only to non-prescription availability.

### **Pharmacovigilance specification**

7. The judgement on benefit risk balance at the time of authorisation is based on limited data. Pharmacovigilance is required because some safety issues will only be detected during normal clinical use. This is due to the established shortcomings of the drug development process, particularly in terms of the size, duration and controlled conditions of clinical trials. The pharmacovigilance “specification” would be a structured method for documenting the established risks of a drug (from pre-clinical and clinical studies), the potential for significant unidentified risks and the potentially at-risk populations and situations that have not been studied pre-approval. This specification will help regulators to identify any need for specific data collection strategies for the post approval period. It will therefore facilitate the construction of the pharmacovigilance plan and risk minimisation plan. Elements of the specification might include:

- identified pre-clinical safety concerns
- any missing pre-clinical data
- ADRs in clinical trials (including seriousness and predictability)
- potential ADRs requiring further evaluation to clarify a risk hypothesis
- populations not studied in the pre-approval phase
- documented interactions
- the potential for unidentified interactions that may occur post-approval
- disease epidemiology
- class effects.

## **Pharmacovigilance plan**

8. There is a need to agree a regulatory requirement for a pharmacovigilance plan prior to granting a marketing authorisation, preferably supported by guidance and a standard format. The plan would be driven by the questions raised by the specification outlined above. The plan would help to better define the safety profile of the drug and would focus on both demonstrating safety as well as identifying harm. The plan would be scrutinised by regulators assessing the marketing authorisation application and would be agreed between the company and the regulator following discussion and modification, prior to granting a marketing authorisation. The plan will then be implemented by the company.
9. For a drug with an extensive pre-approval safety database, including at risk groups, and a well documented safety profile, the pharmacovigilance plan may simply propose that spontaneous reporting systems and periodic safety update reports are sufficient for post approval safety monitoring. However, for products with risks of concern, or with an inadequate pre-approved data safety base, or where at risk groups have not been studied, the plan might detail additional data collection including protocol outlines for post approval safety studies or registries.

## **Risk minimisation toolkit**

10. The strategies for managing risk i.e. a “risk minimisation toolkit” would again be based on the specification. They would be complementary to the pharmacovigilance plan and would focus on practical strategies to minimise risk to patients, i.e. the occurrence of adverse drug reactions. The risk minimisation toolkit might include:
  - SPC and labelling, including population, indication, warnings, contraindications, monitoring
  - communication to healthcare professionals and the public both pre and post launch, including letters, advertisements and educational programmes.
  - Distribution control, including prescription, dispensing, registries and consent
  - treatment protocols and guidelines.

## **Implementation of Risk Management Plans**

11. Recent experience with marketing authorisation applications has highlighted the need for guidance on risk management and clarity of responsibilities.
12. There is a good argument that in order to ensure compliance it should become a regulatory requirement when applying for a marketing authorisation to submit a risk management plan. During the course of implementing the components of the plan, any important emerging risk information will be discussed and the plan revised. A further key aspect of the plan will be the setting of milestones. When these milestones are reached the specification for a particular drug would be modified and the pharmacovigilance plan amended and updated.

## **Initiatives and ongoing work**

13. The International Conference on Harmonisation (ICH) Steering Committee has now endorsed the setting up of a working group to develop a guideline on “prospective planning of pharmacovigilance”. The concepts underlying this ICH Working Group have been mainly driven by the EU regulators and it is anticipated that an ICH guideline will reach step 2 in November 2003. The FDA are also committed to producing detailed guidance on this topic. The World Health Organisation is currently working on risk management in the context of clinical trials.

## **Conclusions and next steps**

14. In view of the need for earlier planning of pharmacovigilance and risk minimisation, this chapter has proposed three key concepts for risk management: a pharmacovigilance specification, a pharmacovigilance plan and a risk minimisation toolkit. In light of the need to have a European position to support the proposals in the 2001 review of legislation and the work within ICH, development of a guideline on risk management plans is high priority. Such guidance has the potential to have a significant positive impact on public health. It is recognised that there are strongly held views on how such plans might best be funded. Nonetheless, further work should be undertaken on the development of a model as a priority.