

# **Pharmacovigilance in Europe: the way forward**

- Views of the CPMP Pharmacovigilance Working Party-

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## ***Executive Summary***

### **Introduction**

Since its creation in 1995, the CPMP Pharmacovigilance Working Party (PhVWP) has worked continuously to improve its practices, both to deal with the ever increasing workload and to contribute harmonisation of regulatory decisions of nationally authorised products. In addition, the PhVWP has worked on the development of strategic tools to enhance pharmacovigilance (PhV) in the EU, including audit of outcomes of the regulatory actions, good vigilance practice, and compliance.

Following the discussion on the EU pharmacovigilance system at the Informal CPMP in October 2001 and at the Groupe de Réflexion in November 2001, and given the above-mentioned experience, a brainstorming group was created within the PhVWP to identify areas in which current practice of pharmacovigilance could be improved. A list of topics to be addressed was approved by the PhVWP. Concepts papers were drafted, compiled and discussed, resulting in the current document.

### **Overall guiding concepts for PhV**

The PhVWP considers that an integrated view on PhV should be fostered. This implies that PhV is to be regarded as a continuous responsibility during the entire life time of a product, i.e. before, at and after authorisation. Whereas there should be reasonable evidence from clinical trial data about the lack of severe noxious effects of a drug at the time of authorisation, post-authorisation studies should be designed to demonstrate its safety in normal conditions of use. As a consequence, the national (NCAs) and EU competent agencies need to work more proactively, such that PhV competent bodies need to participate in safety assessments before and at time of approval in order to plan for necessary and relevant postmarketing surveillance activities. Both within NCAs and at the European level, these activities should be supported by multidisciplinary scientific expertise relevant to the practice of pharmacovigilance.

The MAHs should be given the responsibility to take on an enhanced and continued commitment for post-registration surveillance activities. This would mean an expansion of their PhV framework, including the need to develop new methods, over and beyond spontaneous ADR reporting systems.

### **Organisation at the level of the National Competent Authorities**

The PhVWP finds it crucial that each National Competent Authority (NCA) shall take responsibility to provide adequate competence and resources for handling of PhV issues at the national level. This regards both the general system for safety surveillance of all marketed products and issues related to those products for which the NCA is Rapporteur (R) or Reference Member State (RMS).

Importantly, PhV needs to have a strong national base in order to contribute to effective PhV at the level of the EU. The PhV responsible body of each NCA should be adequately staffed and with sufficient resources.

The PhVWP finds it important to consider particularly some specific aspects of PhV work at the national level.

### *Collaboration in the pre-authorisation and post-authorisation phases*

The need for the MAH to present a risk management plan should be considered from a proactive point of view. At some suitable phase of the process, e.g. day 70, anticipated safety problems of a new product (on the basis of data from e.g. RCTs, on its mechanism of action or on certain biological properties), and consequently the need for an “Early Phase Post Marketing Vigilance”, should be evaluated. Commitments of the MAH to perform safety follow-up studies or initiatives by the NCA to perform intensive monitoring studies are examples of measures that can improve PhV at this stage. In principle, safety sections of the Summary of Product Characteristics (SmPC) should be systematically reviewed by PhV experts. Therefore, PhV competent persons at the NCA should actively participate in the process of approval.

A collaborative approach is also crucial when post-authorisation safety issues are to be discussed at the CPMP level, concerning centrally authorised products (CAPs) and Referrals, or at the PhVWP level concerning mutually recognised products (MRPs) and nationally authorised products (NAPs). Thus, all post-authorisation issues should be discussed jointly both at the national and EU levels using PhV competence in the best possible way.

### *Implementation of variation procedures for NAPs and MRPs at the national level*

During the year 2002 the PHVWP undertook a survey within MSs with the objective of clarifying variation procedures and practices. This initiative was taken based on experiences indicating the existence of barriers and obstacles to the implementation of safety information. The survey showed that the handling of variations differs considerably among MSs, with a range from variations being taken care of solely by the PhV unit to the PhV unit not being involved in the process at all. At the national level there is in general a complaint of lack of resources within the PhV unit and/or dependence of resources at other units. The involvement of national committees can delay the process, and the re-discussion at national level is debatable. Both at national and European level there is lack of transparency. It is difficult to determine when a recommendation is final, and it is difficult to monitor how the procedure is progressing. Class reviews have been particularly difficult to handle. Lack of compliance from the MAH and lack of legal enforcement are other commonly observed problematic issues.

The survey reveals a need to evaluate the organisation, resources, administrative procedures and practices at the national level, with the aim of strengthening the national - and thereby the European - pharmacovigilance competence and efficiency.

### *Crisis management*

A crisis related to a medicinal product in a Member State will usually spread over more Member States or even the whole EU. It may also be the case for a crisis starting during a CPMP referral procedure due to safety reason. Therefore, there is a need for an integrated plan addressing crisis management at national level for NAPs and MRPs as well. All parties that could be involved in a crisis (Commission, EMEA, national agencies, national inspection services) should commit to follow such crisis management plan.

### *Involvement in PMS studies performed by academia*

Collaboration with relevant university departments should be encouraged. One reason would be to give an opportunity of the PhV responsible person(s) to receive scientific training, to exchange research data and to increase the competence at the level of the NCA. Further, a network with university departments can provide the necessary infrastructure and competence to perform safety follow-up studies, e.g. clinical epidemiological studies in the form of intensive monitoring of ADRs for novel drugs.

## **Organisation at the level of the EMEA/CPMP**

### *Mandate of the PhVWP*

The mandate of the PhVWP has been defined in 1995. It is to provide a forum for dialogue between Member States on pharmacovigilance strategy and policy, and to review safety issues at the request of the CPMP for CAPs or for products which are the subject of referrals to the CPMP. Furthermore, the PhVWP reviews the safety of NAPs at the request of NCAs. The PhVWP considers that this mandate should be revised to reflect its current function as a permanent committee of experts for the safety evaluation of all products, as well as its future involvement in pre-authorisation pharmacovigilance.

### *Need for coordinated CPMP-PhVWP meetings*

Communications and exchanges between the CPMP and the PhVWP should be improved. Meeting schedules should allow for co-ordinated CPMP-PhVWP sessions by overlapping meeting dates. Members of the PhVWP (depending on expertise and Rapporteur status of the MS) and the additional scientific experts would participate in the PhVWP meeting during the first 1½ days and thereafter in the CPMP meeting for the next 2½ days. An evaluation of the performance of this system would be needed in an early phase. Adjustments would be made as necessary.

### *Collaboration in the pre-authorisation and post-authorisation phases*

PhV activities at the level of NCAs mentioned in section 3.1. also apply at the CPMP level at the time of approval of CAPs. The CPMP should identify in the pre-authorisation phase domains where additional data collection is necessary for safety reasons, with commitments from the MAH to perform short-term and long-term studies. Timetables, study questions and study protocols should be discussed and approved before authorisation is granted. PhV experts should be involved in the review of the safety sections of the SmPC.

### *Follow-up of PhVWP recommendations*

Experience has shown the difficulties met to implement PhVWP recommendations of actions to be taken by Member States. A timetable is often lacking and it is not often possible to capture if the issue is to be discussed at the level of the CPMP and when the CPMP has finalised its discussions, especially in case of class reviews. The PhVWP recommends to revise the relevant guidelines. It is suggested to introduce at the level of the EMEA a tracking system for each of these issues, in order to keep track of the timetable for the evaluation, decision, implementation and communication process.

## **Role of additional pharmacovigilance expertise**

NCAAs should appoint their PhV expert - one person, or preferably two persons - to serve in the PhVWP on a long-term or permanent basis. This would ensure the opportunity for relevant competence to be provided and developed, and to enable time for preparations and continuity of service, and for collaboration with pre-authorisation staff.

The contribution of additional experts to all aspects of the EU PhV work -PhVWP and CPMP- is considered very useful. Crucially important to the NCAAs is what type of expertise should be provided, the degree of involvement, the role in providing PhV support at the EU and national levels and funding of these experts. These issues need to be urgently resolved, in order for the NCAAs to be able to appoint highly qualified experts with a high level of commitment.

The PhVWP considers that, in general, additional expertise would be more helpful if it concerned domains of knowledge needed for the practice of pharmacovigilance than expertise in pharmacovigilance itself, which is already available at the level of PhVWP. Therefore, there is a greater need for ad-hoc expertise than for the nomination of permanent experts who would attend all PhVWP meetings. Such ad-hoc expertise would include expertise in methods used for assessing the efficacy and safety of drugs (e.g. experts in statistics, pharmacepidemiology, toxicology, genetics, etc.), expertise in drug-related sciences (e.g. experts in experimental and clinical pharmacology, pharmacokineticists), expertise in clinical medicine (e.g. specialists in areas of medicine concerned by a specific issue), and other expertise which may be needed in exceptional circumstances (e.g. experts in information sciences and expert systems). For reasons of efficiency and feasibility, these experts will need to be identified in advance. It is suggested that a General Agreement specifying the process for consultation and the financial arrangements would be contracted by each expert and the EMEA. The experts would remunerated by the EMEA for each expertise, in addition to the reimbursement of travel and hotel costs. A scale of fees could be established by the EMEA according to factors such as speciality, amount of work and complexity of the dossier. For any expertise, the category of fees would be decided by the EMEA in agreement with the chairpersons of the CPMP and/or PhVWP.

Training programs for experts in PhV could be provided by the EMEA for the new experts. It would seem worthwhile that such programs are made available also to the regular PhV experts of the NCAAs.

## **Components of a risk management strategy**

### *Risk detection*

National spontaneous reporting schemes and Periodic Safety Update Reports (PSURs) are currently the main source of information for risk detection. This system is mainly based on spontaneous reporting whose limitations are well-known. For certain safety issues, for certain medicinal products or for certain populations, spontaneous reporting may not be sensitive enough and needs to be supplemented with other permanent sources of information. Moreover, it is unsatisfactory for regulators to base their judgements on a system on which they have a limited control and whose effectiveness may be influenced by a large number of factors, including direct intervention from MAHs to prescribers.

The spontaneous reporting system should be maintained and reinforced in the future. The establishment of a common database for ADRs for all MSs at the EMEA level (Eudravigilance) is considered by the PhVWP a potentially very important resource for improved signal detection. Its full potential requires that tools for data transfer, filing and mining are of adequate performance and quality. Further, the responsibility for signal detection in the data-base needs to be clearly defined, whether it should be up to special staff of the EMEA, assessors at the responsible NCAs, or a collaborative effort. The PhVWP proposes that the database would be screened, with the help of sophisticated data mining tools, for possible new signals that would be further evaluated by the PhVWP on a regular basis.

There are many situations where intensified early post-marketing surveillance is necessary. Studies for intensive and early monitoring could substantially help to quickly characterise the risk and effect profiles of novel drugs, identified in the pre-authorisation phase to have a particular need for safety follow-up. NCAs should explore the possibility to perform such short-term postmarketing studies in collaboration with relevant clinical and academic departments, and preferably independently of the MAH. Single MSs may contribute useful information from national data; an efficient strategy would be to establish a network of academic units in different MSs. Rapporteur MSs would have the lead responsibility for the particular product. Such system would benefit from EU funding.

### *Risk quantification*

Risk quantification normally requires formal epidemiological studies to be performed, in order to provide valid and precise measures of frequency and association. One cost efficient way would be to monitor intensely during a few initial years the patients who are prescribed the particular drug within a defined clinical setting. Such post-marketing intensive monitoring studies for selected new drugs should ideally be performed by academic departments in collaboration with pharmacovigilance units of the NCAs to produce optimally reliable scientific result. However, this system is difficult to be used for older products and cannot provide results within short timeframes, unless there exist efficient and validated data sources. 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 pharmaco-epidemiological purposes. For databases commonly used, the population characteristics should be compared to characteristics of the populations in other European countries, in order to assess to which extent results from such databases can be inferred to other countries.

Although there are a number of good databases in the European Union, they are still scarce. National agencies must support (or lead) such important developments. Formal agreements with the institutions running the databases (e.g. GPRD, IMS) will be essential in the near future, in order to assure access to the raw data and/or with the epidemiological teams with experience in conducting studies using such databases. Such agreements (including funding) should be made by national agencies and/or the EMEA. The custom of yielding the MAHs the whole responsibility to carry out such studies should be revisited.

Other potential sources of information to be developed are registries (which address specific diseases frequently associated with drugs, such as haematological dyscrasias or severe hepatic and skin disorders) and follow-up programs (which address certain populations, such as pregnant women, or populations exposed to special medicinal products, such as biologicals or xenogeneic cellular products). The methodological framework for registries or follow-up



programmes of patients treated with a medicinal product should be developed in order to gain time in the development of protocols, registration documents, follow-up procedures, ADR notification procedures, etc.

### *Risk assessment*

The safety profile of a product is assessed based on a pooled analysis of all human safety data, including, where appropriate, preclinical data. Risk assessment requires the ability to put in perspective the safety profile of the drug taking into account the safety profile of alternative drugs, to identify the data needed to properly evaluate the risk depending on the level of future exposure and the severity of the treated disease, and to identify the strategy for monitoring the adverse effects and to define the appropriate PhV actions. Risk assessment is the area where external expertise has been most often used by agencies until now. With an increasing proportion of innovative substances, often licensed on the basis of very limited clinical data, PhV needs to be more effective and able to detect safety signals rapidly. PhV staff therefore need to have good knowledge of the pre authorisation dossier.

The following proposals are made: a) at a national level, rapporteurs, co-rapporteurs and reference member states should involve the PhV experts in the licensing assessment, b) at the European level, PhV experts should participate at the CPMP and its various working parties.

### *Risk minimisation*

This phase includes the adoption and follow-up of administrative measures, the communication of risks and the implementation of prevention strategies. The need for strengthening of PhV work during the pre-authorisation phase, rationale for risk management plans and for early phase post marketing vigilance were discussed above. Despite this licensing assessment, in recent years there has been an increase in the number of major drug safety issues identified soon after marketing. This highlights the crucial role of the PhV assessor in the pre-authorisation phase. The PhV assessor can utilise his or her expertise in safety issue detection and assessment to minimise the chances of safety issues being missed at the time of licensing and can recommend risk reduction strategies for the post-authorisation phase. Furthermore, the PhV assessor can identify areas where data are lacking (and hence where safety issues may arise) and recommend the need for studies in the post authorisation phase.

Difficulties experienced by Regulatory Authorities to implement decisions and follow-up on recommendations in the post-authorisation phase have been delineated above, and proposals have been made both at the national and the European level. It needs to be emphasised that amendments of the pharmaceutical legislation is a prerequisite for the effective enforcement of different types of post-authorisation commitments.

### *Risk communication*

Evaluation of safety information relating to medicines results in an evaluation/outcome which needs to be communicated as appropriate, in a systematic way to the relevant parties e.g. to other agency departments and expert groups, MAHs, EMEA, other Regulatory Authorities, WHO, healthcare professionals, patient groups, the general public and the media. The provision of communications relating to the safety of medicines has the potential to significantly impact on the general public, particularly if the safety issue concerned has a

broad public health interest, e.g. an issue related to the use of childhood vaccines. Strategies for risk communication based on EU PhV regulation are clearly needed and would greatly benefit the consumers of each MS. Greater efforts to avoid scare effects and irrational behaviours through communications tailored for particular audiences, proactive and co-ordinated releases are urgently needed. Risk communication on a national level will increasingly depend on information from EU PhV work, either through the CPMP or directly from the PhvWP.

## **Audit of decision making and monitoring of outcomes**

### *Audit of the decision-making process*

Every effort must be done to follow best practice in PhV. It is therefore important to gain knowledge of obstacles to be overcome and to measure the effectiveness and impact (over-all and for different steps) of regulatory actions. Standards should be defined and agreed, and the performance should be measured. The experience gained during the process and throughout the years should be evaluated with the aim of improving PhV in areas where activities are yet inadequate. The PhVWP has identified and described major steps in PhV that need to be audited and how such audit could be performed. In particular, auditing should address all aspects of data management and communication, incl. data collection, processing, retrieval and analysis, assessment and interpretation of reports, risk/benefit evaluation and signal generation.

### *Monitoring outcomes of regulatory decisions*

The effectiveness of regulatory decisions is a key element for the ability of PhV systems to protect public health. Measures taken to improve the safe use of a drug need to be rapidly assessed and corrected as necessary. NCAs and the EMEA should establish a system to collect and evaluate data allowing to assess the effectiveness of communication to health professionals and to patients (and to identify barriers to it), to evaluate the level of compliance of prescribers and patients to recommendations, to assess the impact of regulatory decisions on morbidity/mortality, to identify implementation failures at an early stage and to decide additional actions as necessary. This system should also be designed as an on-going learning process on how to deal effectively with drug safety hazards, e.g. how to improve communication strategies. The knowledge gained through a critical examination of previous experience should normally be translated into a change of practice and procedures.

## **Conclusion**

In the view of the PhVWP, there is a great potential for improvement of PhV to the benefit of public health. The manifold detailed strategies will need much work to be developed and realised, both at the levels of MS and of the EMEA. The PhVWP is prepared to contribute in all relevant aspects of the forthcoming work.

## ***1. Introduction***

Since its creation in 1995, the CPMP Pharmacovigilance Working Party (PhVWP) has worked continuously to improve its practices, both to deal with the ever increasing workload and to contribute harmonisation of regulatory decisions of nationally authorised products. In addition, the PhVWP has worked on the development of strategic tools to enhance pharmacovigilance (PhV) in the EU, including audit of outcomes of the regulatory actions, good vigilance practice, and compliance.

Following the discussion on the EU pharmacovigilance system at the Informal CPMP in October 2001 and at the Groupe de Réflexion in November 2001, and given the above-mentioned experience, the Chair person of the PhVWP proposed to hold a brainstorming meeting on 23 January 2002 to discuss general pharmacovigilance and organisational issues of the PhVWP. The PhVWP welcomed this idea. A Drafting group was created within the PhVWP to identify areas in which current practice of pharmacovigilance could be improved. It was agreed that the following topics would be further addressed:

- General organisational matters (including internal communication at national level and liaison with the CPMP)
- Role of pharmacovigilance in the pre-submission and marketing authorization evaluation phase
- Integration of further expertise in pharmacovigilance activities
- Signal detection tools and early marketing phase pharmacovigilance
- Assessment of PSURs and performance of class-reviews
- Conduct of pharmacovigilance and Urgent Safety Restrictions for centrally authorised products
- Conduct of pharmacovigilance and Urgent Safety Restrictions for mutually recognized and purely nationally authorised products
- Crisis management
- Interaction with academia.

The Drafting Group members prepared concepts papers as key elements for revision of procedures and guidance documents. Discussions were held in subsequent PhVWP meetings. Several drafts were compiled and discussed, resulting in the current document.

## ***2. Overall guiding concepts for PhV***

The PhVWP considers that an integrated view on PhV should be fostered. This implies that PhV is to be regarded as a continuous responsibility during the entire life time of a product, i.e. before, at and after authorisation.

Whereas there should be reasonable evidence from clinical trial data about the lack of severe noxious effects of a drug at the time of authorisation, post-authorisation studies should be designed to demonstrate its safety in normal conditions of use. As a consequence, the national (NCAs) and EU competent agencies need to work more proactively, such that PhV competent bodies need to participate in safety assessments before and at time of approval in order to plan for necessary and relevant postmarketing surveillance activities. Both within NCAs and at the European level, these activities should be supported by multidisciplinary scientific expertise relevant to the practice of pharmacovigilance.

The MAHs should be given the responsibility to take on an enhanced and continued commitment for post-registration surveillance activities. This would mean an expansion of their PhV framework, including the need to develop new methods, over and beyond spontaneous ADR reporting systems.

### ***3. Organisation at the level of the National Competent Authorities***

The PhVWP finds it crucial that each National Competent Authorities (NCA) shall take responsibility to provide adequate competence and resources for handling of PhV issues at the national level.

This regards both the general system for safety surveillance of all marketed products and issues related to those products for which the NCA is Rapporteur (R) or Reference Member State (RMS).

Importantly, PhV needs to have a strong national base in order to contribute to effective PhV at the level of the EU. The PhV responsible body of each NCA should be adequately staffed and with sufficient resources.

The PhVWP finds it important to consider particularly some specific aspects of PhV work at the national level.

#### **3.1. Collaboration in the pre-authorisation and post-authorisation phases.**

##### *3.1.1. Background*

Pharmacovigilance includes risk management activities which attempt to minimise the morbidity and mortality from adverse reactions to marketed medicines and hence maintains a positive balance of risks and benefits for products on the market.

The safety profile of a product is assessed based on a pooled analysis of all human safety data, taking into account the preclinical data. It needs to be updated by a continuous evaluation. At present the licensing 'pharmacovigilance' assessments are in general made by clinical assessors rather than by assessors experienced in pharmacovigilance.

##### *3.1.2. Collaboration in the pre-authorisation phase*

Despite this licensing assessment, in recent years there has been an increase in the number of major drug safety issues identified soon after marketing. This highlights the crucial role of the pharmacovigilance assessor in the pre-authorisation phase. The pharmacovigilance assessor can utilise his or her expertise in risk detection and assessment to minimise the chances of safety issues being missed at the time of licensing and can recommend risk reduction strategies for the post-authorisation phase:

- they are able to put in perspective the safety profile of the drug taking into account the safety profile of alternative drugs;
- they can identify the data needed to properly evaluate the risk, depending on the level of future exposure and the severity of the treated disease;
- they can identify areas where data are lacking, and hence where safety issues may arise;
- they are able to identify the strategy for monitoring the adverse effects and to define the appropriate pharmacovigilance activities before marketing of the product, e.g. to recommend the need for studies in the post authorisation phase .

It is therefore proposed that at the national level, rapporteurs, co-rapporteurs and reference member states should involve pharmacovigilance experts in the licensing agreement.

In the period between the submission of the marketing authorisation application, but prior to authorisation, routine single case expedited reporting is not required except according to national law where the product is being used in a clinical trial. However, in the pre-authorisation period, information which impacts on the benefit/risk evaluation may become available from the applicant, from member states where the drug is already available on a compassionate use basis, or from countries where the drug is marketed. This information should be immediately submitted by the applicant to the competent authority of the member states where the application is under assessment, and in the case of a centralised application to the EMEA, rapporteur and co-rapporteur. Pharmacovigilance experts should be involved for the evaluation of such reports.

### *3.1.3. Role of pharmacovigilance experts for assessing SPCs*

The benefit/risk is evaluated during the pre marketing phase. The risk estimation is based on all available scientific data, but also takes into account risk reduction strategies including information in the SPCs. Safety sections of the SPC should be systematically reviewed by pharmacovigilance experts, in line with the Guideline on the Summary of product Characteristics (European Commission, December 1999), which is currently being revised.

### *3.1.4. Collaboration in the post-authorisation phase*

With an increasing proportion of innovative substances, often licensed on the basis of very limited clinical data, pharmacovigilance need to be more effective and able to detect safety signals rapidly. Pharmacovigilance staff therefore need to have good knowledge of the pre authorisation dossier.

## **3.2. Implementation of variation procedures at the national level**

### *3.2.1. Introduction*

At the PhVWP meeting in January 2002 it was decided to carry out a survey within MSs in order to clarify variation procedures and practices in the different MSs, with Denmark acting as the Rapporteur. This initiative was taken based on experiences indicating the existence of barriers and obstacles to the implementation of safety information.

The main purpose of the investigation was to check if recommendations from the PhVWP are actually carried out and to identify barriers and obstacles at the national level in the process of implementation. In particular, a need for clarification of variation procedures for implementation of recommendations from the PhVWP in SPCs for nationally and mutually recognised medicinal products was deemed necessary. The procedures for centrally authorised products was not included in this survey. It was proposed to perform a retrospective analysis based on previously given recommendations, e.g. concerning fluoroquinolones and hepatotoxicity, fluoroquinolones and cardiotoxicity and NSAIDs and infertility.

This chapter summarises the responses from the MSs which have responded.

### 3.2.2. Questions raised

**Q1:** Please give a brief description of the procedure by which the pharmacovigilance unit at your agency implement PhVWP recommendations for SPC changes for nationally and mutually recognised medicinal products, including the interaction with relevant involved parties (e.g. other units at the agency, industry).

**Q2:** Please provide information of the status (procedure *not initiated*, *initiated*, *finalised*) and duration of the variation procedure concerning implementation of PhVWP recommendations for e.g.

a: levofloxacin and hepatotoxicity (October 2001)

b: NSAIDs and infertility (September 2001)

c: fluoroquinolones and cardiotoxicity (June 2001)

**Q3:** Please provide information of main barriers and obstacles identified during the process(es)

**Q4:** Please describe how the forthcoming implementations of SPC changes for the dopaminergic substances, warranted by the reports of sleep attacks, will be carried out. If the procedure does not differ from the procedure described above, then just make a cross-reference to section Q1

**Q5:** Please provide any other information considered relevant for this issue.

### 3.2.3. Summary of the responses from Member States

#### Q1:

- The handling of variations within MSs differs in several aspects.
- In some MSs the variation procedure is handled within the Pharmacovigilance Unit, without the involvement of other units within the agency. This is the case in BE, GR, IT, ES and SE.
- In FR the Pharmacovigilance unit at the agency initiates the process, but the variation application is evaluated by the regional Pharmacovigilance centres.
- In some MSs – FI, IE and the UK – the variation is handled by the Pharmacovigilance unit and the registration unit in co-operation.
- In some MSs the variation procedure is handled outside the Pharmacovigilance unit, e.g. by the registration / approval unit. This is the case in DK, NL, NO and PT.
- In some MSs – BE, FR, GR, IT and possibly PT – the recommendations are evaluated in and the final decision is taken by a national committee.

#### Q2a:

- Most MSs are involved in the Mutual Recognition procedure and state, that the procedure is not initiated (BE, DK, ES, FI, IT, and SE); UK is apparently the RMS and states that the procedure is initiated.
- The procedure is not initiated in GR, IE or PT; no further explanation is provided.
- FR has not adopted the recommendations, as a national inquiry resulted in conclusions different from the conclusions reached by the PHVWP.
- The status is unknown in NL.
- The product is not marketed in Norway.

**Q2b:**

- In most MSs the procedure is not initiated (BE, DK, FI, IE, PT, UK, ES); in three cases it is stated that – due to the high number of products and MAHs involved, and due to several different aspects being discussed currently – the variations will be handled on a case by case basis and simultaneously with other variations.
- In one MS (FR) the procedure is partly initiated.
- In 2 MSs (IT and SE) the procedure is initiated.
- In one MS (NL) the status is unknown.
- NO states “not implemented”.

**Q2c:**

- In most MSs the procedure is not initiated (BE, DK, FR, IE, IT, PT, ES, SE);
- In one MS the procedure is initiated (UK)
- One MS (FI) state, that the procedure is initiated for nationally authorised products, but not for MR – products.
- In one MS (NL) the status is unknown.
- NO states “not implemented”.

**Q3:**

Examples of obstacles and barriers seems to be

- at the national level:
- lack of resources within the Pharmacovigilance unit
- dependence of resources in other units
- lack of transparency with respect to ongoing procedures
- difficulties to monitor how the procedure is progressing
- lack of compliance from the MAH (delay, disagreement)
- lack of legal tools to impose the SPC changes
- the involvement of national committees in some MSs (delay, disagreement)
- for class reviews separate aspects has to be taken into consideration
- problems regarding linguistic translations
- the large variation in quality / quantity of SPCs/PILs of medicinal products containing the same active substance
  
- at the European level:
- lack of transparency as to whether or not the recommendations are final
- uncertainty with respect to the need for awaiting a discussion / decision in CPMP
- lack of transparency as to whether or not the RMS has initiated the procedure
- lack of communication between authorities and MAHs
- the PHVWP agreed wording is revisited by MSs at a national level
- the observation that MAHs may (re)act differently in different MSs (e.g. oral contraceptives)
- insufficient legal framework to enforce the European SPC wording at the national level

**Q4:** In most cases cross reference is made to Q1

**Q5:** It is proposed to establish a Best Practice Guide (SE)



### 3.2.4. Conclusions

The survey showed that the handling of variations differs considerably among MSs, with a range from variations being taken care of solely by the PhV unit to the PhV unit not being involved in the process at all. At the national level there is in general a complaint of lack of resources within the PhV unit and/or dependence of resources at other units. The involvement of national committees can delay the process, and the re-discussion at national level is debatable. Both at national and European level there is lack of transparency. It is difficult to determine when a recommendation is final, and it is difficult to monitor, how the procedure is progressing. Class reviews have been particularly difficult to handle. Lack of compliance from the MAH and lack of legal enforcement are other commonly observed problematic issues.

The survey reveals a need to evaluate the organisation, resources, administrative procedures and practices at the national level, with the aim of strengthening the national - and thereby the European - pharmacovigilance competence and efficiency

### 3.3. Crisis management

A crisis management plan for centrally authorised product has been laid down in a EMEA/CPMP document of 24 September 1997 (ref. CPMP/388/97). There is not only a need to update this document to take on board management changes within the EMEA and national agencies, but also the scope of the document should be widened by addressing crisis management for medicinal products approved through Mutual Recognition and National procedures as well.

Once a crisis related to a medicinal product is evolving in a Member State it will usually spread over more Member States or even the whole EU by media activity. It may also be the case that a crisis related to a medicinal product starts during a CPMP referral procedure (based on Article 31 or 36 of Directive 2001/83/EC) for that product because of a safety issue. In such a crisis situation there is a role to play for both the EMEA/CPMP and national agencies. So, an integrated crisis management plan regarding both centrally and nationally (incl. MR) authorised product is definitely needed.

All parties which could be involved in a crisis (Commission, EMEA, national agencies, national inspection services) should commit themselves to the new crisis management plan.

### 3.4. Involvement in PMS studies performed by academia

Since new medicinal products can only be tested through clinical trials in a limited number of patients and for a limited amount of time, knowledge on effects and adverse reactions of new drugs is incomplete at the time when they are first released on the market. In particular, novel drugs that are designed to work through new biological principles, e.g. biotechnological products, may give rise to serious and unpredictable adverse reactions that can be detected only after the drug has been used on the market by sufficiently many patients for a sufficiently long time in the clinical setting. There is an obvious need to obtain as quickly as possible adequate information to define the safe and rational use of the new drug. One cost efficient way would be to monitor intensely during initial years the patients who are prescribed the particular drug within a defined clinical setting. Such post-marketing intensive monitoring studies for selected new drugs should ideally be performed by academic

departments in collaboration with pharmacovigilance units of the NCAs to produce optimally reliable scientific result, independently of an influence by the MAH.

The issue is by which mechanism MAHs could co-operatively - all companies with products of a class of new-concept drugs - sponsor studies performed in academic departments and utilised by NCAs so that independence of data is accomplished and conflict of interest avoided.

A discussion on the prospects for this model was initiated jointly at the MPA and Karolinska Institute in Sweden in the year of 2000 and continued among MSs within the PhVWP of the CPMP February 2001.

#### Examples of model studies

In Sweden two studies are ongoing that illustrate the design, logistics and usefulness of post-marketing intensive monitoring studies in a clinical setting.

**\*TNF blocker project.** Patients who were prescribed the new TNF blockers Enbrel and Remicade before approval and through the license procedure in Sweden were registered and included in a cohort for follow-up. The cohort includes around 1 000 patients who have been monitored by their responsible physicians in all 30 special clinics providing specialist rheumatological care. Data obtained during follow-up were entered in computerised forms, and later examined to define possible ADRs. Also after MA was granted, follow-up of the registered patients has continued, generating extensive data on events to be evaluated.

The project has a steering group with representatives of the Department of Rheumatology of the Karolinska Institute, the Swedish Society for Rheumatology and the agency (MPA).

The study has been funded by the County Councils and by the Swedish National Board of Health and Welfare, however for shorter periods and without continuity.

**\* HIV drug project.** Over 1 000 patients have been included in a monitoring study at four of the main clinical departments (three in Stockholm, one in Lund) responsible for the care of HIV patients. Detailed information has been collected firstly through a cross-sectional approach by abstracting information on exposures and events from the medical records, and, secondly, by following these patients longitudinally to monitor all new suspected ADRs. A substantial amount of new data has been generated on e.g. the development of changes in the fat distribution and on metabolic events.

This project has been financed only irregularly by public institutions and by the MPA. The progress of the project is however hampered by the instability and insufficiency of the funding.

These two ongoing post-marketing studies illustrate the utility of this type of studies for pharmacovigilance that are carried out for a duration of a few years. They constitute in Sweden a new model for an intensive monitoring of ADRs of selected new drugs which has the potential to produce in an expedient and cost effective way data on both effects and ADRs soon after the drug has been introduced on the market. Such studies would thus provide an added value to the existing spontaneous reporting systems.

For some of the newly introduced drugs it seems particularly urgent to collect quickly and efficiently high-quality safety data. Examples of such drugs are the new selective NSAIDs and the new immuno-modulators for which the spontaneous reporting system gives reason for suspicions on new and serious ADRs. It is clear that drugs being developed from molecular genetic research will be important targets for such intensive monitoring systems.

In the current discussion within the EMEA and among MSs it is generally recognised that the capability of pharmacovigilance systems needs to be enhanced. Intensive monitoring studies

in academic settings may be one valuable approach to make post-marketing safety follow-up more efficient and reliable.

The experience in Sweden pinpoints one obstacle in managing this type of studies, the lack of continuous and adequate funding. The progress and optimal completion can not be accomplished in the absence of adequate financial support. Public institutions do not seem to be in a position to fully fund post-marketing studies. Furthermore, applications for grants are very time consuming and their outcome unpredictable. At this time it is not possible for the MPA of Sweden to require additional fees from particular concerned MAHs for these types of ad hoc studies. In the Swedish experience, MAHs can be motivated to support such studies, jointly with other companies marketing brands within the same class of compounds. It is reasonable that the MAHs have an interest in the production of data that are collected quickly, completely and reliably and that could form a more solid and reliable basis for risk-benefit evaluations than could data from spontaneous reporting systems.

This proposal suggests that all MAHs for a particular class of new drugs of interest for a new post-marketing monitoring study would be asked to provide jointly the necessary funds. The key issues are how to safeguard the independence of the academic department in performing the study and interpreting and publishing the results and how to avoid a real conflict of interest when the data are to be used for regulatory decisions.

Agreements on MAH funding of independent projects would conform to the following principles:

- concerned MAH companies shall be approached jointly and requested to provide their contributions of funds. The size of the grant would tentatively be determined by the total budget and the market share of the respective company, or according to other type of agreement between the companies;
- the specific research project shall be managed and administered by a committed academic department in collaboration with the pharmacovigilance unit of the MPA;
- the conduct of the study shall be lead by a scientific steering group, to be chaired by the chairman or other appointed member of the concerned academic department and consist of representatives of the academic disciplines and professional society that the particular project requires and of the regulatory agency. The steering group shall be responsible for all decisions on the design, conduct, data collection, data analyses and interpretation and scientific reporting of results. When necessary scientific advice can be obtained from external academic representatives of relevant competence. The MAHs may send an observer to the steering group meeting;
- the scientific publication of obtained results shall follow the deliberations by the steering group alone. The concerned MAHs will have access to periodic compilations of registered ADRs according to specific agreements and to the eventual final peer reviewed and accepted scientific manuscripts, for comments;
- the regulatory agency has the right to use all registered data and prepared scientific manuscripts resulting from the project as knowledge base for regulatory decisions when necessary.

## ***4. Organisation at the level of the EMEA/CPMP***

### **4.1. Mandate of the PhVWP**

The mandate of the PhVWP has been defined in 1995. It is to provide a forum for dialogue between Member States on pharmacovigilance strategy and policy, and to review safety issues at the request of the CPMP for CAPs or for products which are the subject of referrals to the CPMP. Furthermore, the PhVWP reviews the safety of NAPs at the request of NCAs. The role of such party is, however, a bit fuzzy and should be more clearly defined and reinforced, both functionally and legally.

The PhVWP considers that this mandate should be revised to reflect its current function as a permanent committee of experts for the safety evaluation of all products, as well as its future involvement in pre-authorisation pharmacovigilance.

### **4.2. Need for coordinated CPMP-PhVWP meetings**

Communications and exchanges between the CPMP and the PhVWP should be improved. Meeting schedules should allow for co-ordinated CPMP-PhVWP sessions by overlapping meeting dates. Members of the PhVWP (depending on expertise and Rapporteur status of the MS) and the additional scientific experts would participate in the PhVWP meeting during the first 1½ days and thereafter in the CPMP meeting for the next 2½ days. MS The PhVWP finds it feasible to implement this new order from January 2003. An evaluation of the performance of this system would be needed in an early phase. Adjustments would be made as necessary.

### **4.3. Collaboration in the pre-authorisation and post-authorisation phases.**

PhV activities at the level of NCAs mentioned in section 3.1. also apply at the CPMP level at the time of approval of CAPs. The CPMP should identify in the pre-authorisation phase domains where additional data collection is necessary for safety reasons, with commitments from the MAH to perform short-term and long-term studies. Timetables, study questions and study protocols should be discussed and approved before authorisation is granted. PhV experts should be involved in the review of the safety sections of the SmPC.

A collaborative approach is also crucial when post-authorisation safety issues are to be discussed at the CPMP level, concerning centrally authorised products (CAPs) and Referrals, or at the PhVWP level concerning mutually recognised products (MRPs) and nationally authorised products (NAPs). Thus, all post-authorisation issues should be discussed jointly both at the national and EU levels using PhV competence in the best possible way. Pharmacovigilance experts should therefore participate at the CPMP and its various working parties.

### **4.4. Follow-up of PhVWP recommendations**

#### 4.4.1. Background

The responsibility for conduct of pharmacovigilance of MR products and purely national authorised products rests with the competent authorisation of all individual member states who have granted the authorisation. The guidelines for the procedures of MR products are given in *Vol 9 Rules Governing Medicinal Products in the European Community: 2.3 Conduct of pharmacovigilance for medicinal products authorised through the mutual recognition procedure*. For purely national procedures, the guidelines are given in *Vol 9 Rules Governing Medicinal Products in the European Community: 2.1 Procedure for competent authorities on the undertaking of pharmacovigilance activities*. The last one being a guideline on pharmacovigilance activities in general.

A problem has been the follow-up and implementation of recommendations given by PhVWP (and adoptions by CPMP after Referral procedures) on national level concerning MR products and nationally authorised products. Experience of the PhVWP for some years (see section 3.2) has shown a need for a revision or a supplement of relevant guidance documents.

#### 4.4.2. Implementation procedures – point for improvement

The two guidance documents are describing the process from ADR reporting and signal generation, through the process of evaluation, and finally to the recommendation of actions to be taken by MAH and competent authorities. However, the implementation procedure per se is not described in the documents. Several aspects can be improved.

- a time table is mostly lacking and it may be difficult to capture when the final recommendation is given by the PhVWP;
- how to know if the issue also are to be discussed further at the level of CPMP before the implementation process is to be started, particular in the case of class-reviews;
- if to be discussed at the CPMP, how to capture that the final recommendation has been given by CPMP and how to know if the implementation issue have to wait for a Commission decision ?

#### 4.4.3. Need for revision of guidance documents

The implementation procedure should be described in the documents (paragraph 3.3 in 2.3 Conduct of pharmacovigilance for medicinal products authorised through the mutual recognition procedure and in paragraph 4 in 2.3 Conduct of pharmacovigilance for medicinal products authorised through the mutual recognition procedure):

When a new pharmacovigilance issue is identified, either in the PhVWP or in the CPMP, a time table should be set for the evaluation, decision, implementation and communication process, if possible. This should be reflected in the Drug Monitor, which is updated every PhVWP meeting. As part of the final recommendation, a time table for the implementation and communication process should be suggested.

To facilitate the whole procedure we might introduce a form for tracking these issues. The form could be used in the Drug Monitor, and should be added in the Appendix in the Final Minutes from the PhVWP.

*Draft of a tracking form for the conduct of pharmacovigilance concerning products in MRP and nationally authorised products (NP)*

<p>Issue:</p> <p><input type="checkbox"/> An issue concerning a class of drugs</p> <p><input type="checkbox"/> An issue concerning a single substance</p> <p><input type="checkbox"/> New signal</p> <p><input type="checkbox"/> Variation</p> <p><input type="checkbox"/> Referral</p>
<p>Evaluation and decision procedure - time table:</p> <p>PhVWP – recommendations:</p> <p>Date:</p> <p>CPMP- recommendation/adoption:</p> <p>Date:</p> <p>Commission decision:</p> <p>Date:</p>
<p>Implementation and communication procedure – time table:</p>

#### **4.5. Conduct of PhV and Urgent Safety Restrictions for CAPs**

##### *4.5.1. Introduction*

The paper on conduct of pharmacovigilance for centrally authorised products describes the legal framework for monitoring of centrally authorised products, the functions and procedures for conducting pharmacovigilance for the products and the specific roles of the various parties involved (CPMP, PhVWP, Rapporteur, Co-Rapporteur, EMEA, MAH and European Commission). In light of experience gained with monitoring the safety of centrally authorised products and in the context of discussions to strengthen pharmacovigilance, a number of issues have been identified which should be taken into account in updating this document.

##### *4.5.2. Obligations of the MAH*

- It may be appropriate to revise this section to cross refer to the NtMAH (1.4.2.5.2), to reflect the possible need for increased PSUR reporting.
- Other revisions may be necessary to reflect comments on handling PSURs.

##### *4.5.3. Pre-authorisation issues*

- Reference to pharmacovigilance arising in the pre-authorisation period is mentioned in the document (3 – Principles, 4.1 – Reporting ADRs, 4.3.1 – Hazards in the Pre-

Authorisation Phase). In order to facilitate a more integrated approach to pharmacovigilance, the document should be amended to reflect the need for a contribution from a pharmacovigilance perspective during this period.

#### *4.5.4. EudraVigilance*

- The potential for the EudraVigilance database to serve as a signalling function should be reflected in the document. It may also be considered appropriate to define a timescale for review of signals by the PhVWP (see section 6.2.2. of this document).

#### *4.5.5 PSURs & Post Authorisation Studies*

- Point 1 above (Obligations of the MAH) also applies here.
- The timescale for implementation of variations agreed by PhVWP/CPMP, outside the Urgent Safety Restriction (USR) has been previously discussed. Consideration should be given to the possibility of reducing the time required to issue a European Commission Decision, following adoption of the Opinion.

#### *4.5.6. Post Authorisation Commitments*

- Experience has shown differences and delays with regard to implementation of post-authorisation commitments. It is suggested that the document could be updated to reflect the need to meet these commitments, prior to issue of the Marketing Authorisation.

#### *4.5.7. Drug Monitor*

- Reference is made to a specific tracking system similar to the existing drug monitor “*to be introduced and reviewed on a regular basis by the PhVWP*”. At present just one drug monitor is used for tracking safety issues with all products, regardless of the system of authorisation and it is suggested that this section should be reworded to remove the implication that a second system exists for centrally authorised products.

## ***5. Role of additional pharmacovigilance expertise***

### **5.1. Introduction**

The contribution of additional experts to all aspects of the EU PhV work -PhVWP and CPMP- is considered very useful. Crucially important to the NCAs is what type of expertise should be provided, the degree of involvement, the role in providing PhV support at the EU and national levels and funding of these experts. These issues need to be urgently resolved, in order for the NCAs to be able to appoint highly qualified experts with a high level of commitment.

### **5.2. What do we mean by "expertise" ?**

It is generally accepted that pharmacovigilance is, broadly speaking, the process of detecting, evaluating and preventing drug-related health hazards with the final objective of protecting public health. It is also increasingly recognised that the pharmacovigilance process should start before the marketing of the drug, hereby extending the life span of the drug to be covered. Where fully implemented, this process embraces many different activities such as toxicological and epidemiological investigations, statistical analysis, benefit-risk evaluation, regulatory decision-making, communication, etc... Pharmacovigilance therefore requires the collection and integration of various technical knowledge and inputs. However, it should be recognised that pharmacovigilance has not (yet) developed an extensive body of knowledge of its own.<sup>1</sup>

This view has several implications with regards to expertise:

- Pharmacovigilance should not be viewed as a "science" (i.e. a systematised body of theoretical knowledge) but as a "discipline" (i.e. a field of practice of scientific knowledge).<sup>2</sup>
- As a field of practice, pharmacovigilance does not lend easily itself to entering academic curricula (existing courses of "pharmacovigilance" are most often courses of pharmaco-epidemiology and/or pharmacology); it also explains the small number of people trained in pharmacovigilance outside regulatory authorities and the pharmaceutical industry.
- The exercise of pharmacovigilance is based on the collection and use of scientific knowledge; it is essentially a matter of skill in addition to knowledge. This skill is gained by experience and increased by practice.<sup>3</sup> It is also enhanced by the sharing of experiences through learned societies and meetings such as the PhVWP.
- As expertise in pharmacovigilance is primarily based on practice, there is only a limited number of experts in pharmacovigilance outside regulatory authorities and the pharmaceutical industry.

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<sup>1</sup> Aspects related to spontaneous reporting and under-reporting probably represent the most specific pharmacovigilance knowledge.

<sup>2</sup> Note that this view is not compatible with WHO's definition of pharmacovigilance, which describes it as a Science.

<sup>3</sup> It is noteworthy that pharmacovigilance experts are generally primarily engaged by regulatory authorities or drug companies for their knowledge in areas such as drug regulatory environment, toxicology, pharmacology, pharmaco-epidemiology or internal medicine; it is accepted that their expertise in pharmacovigilance will be acquired with experience.



- Additional expertise for the PhVWP would be most helpful if it concerned one of the domains of knowledge needed for the practice of pharmacovigilance. Accordingly, there is a greater need for expertise *for* pharmacovigilance than for expertise *in* pharmacovigilance.

### 5.3. Why does the PhVWP need additional expertise ?

There are several reasons why additional expertise may be needed, and some of them are suggested below. They are not mutually-exclusive and certainly not all-inclusive.

- *Domains of knowledge are inadequately represented at the level of the PhVWP.* As mentioned above, the practice of pharmacovigilance requires integrating various domains of knowledge and information. Not all of these domains can be represented in a group of about twenty delegates. The majority of delegates have an expertise in pharmacovigilance as defined above, but many fields are not covered. Expertise in pharmacogenetics and biotechnology are examples of specific knowledge which cannot be routinely present during pharmacovigilance meetings. An update of the domains of expertise currently available at the PhVWP should be performed
- *The workload for the PhVWP members is an obstacle to an in-depth evaluation of technical dossiers.* The heavy workload both at the national level and at the European level for preparing the PhVWP meetings may not leave enough time for a thorough evaluation of complex dossiers, including the need for literature review and investigation of related issues. The PhVWP could delegate to an outside expert the evaluation of such dossiers.
- *PhVWP members represent their health authority.* PhVWP members are nominated by their health authority and may be expected to convey to the PhVWP the opinion and recommendations expressed by their national advisory committee. This ambiguous position may obscure the role of the PhVWP as an expert group and may be viewed detrimental to the exercise of pharmacovigilance according to purely scientific principles. Experts nominated by the EMEA (rather than by a national authority) would have a certain degree of scientific independence. In some situations, they could be helpful for assessing scientific issues, irrespective of national or regulatory considerations.
- *Activities of the PhVWP are focussed on regulatory decision-making.* Although the focus on regulatory decision-making is not explicit in the "Mandate for a permanent CPMP working group on Pharmacovigilance" (March 1995), the work of the PhVWP has shifted to that direction. Even if this trends is understandable, it may be detrimental to other activities such as the identification of research priorities, the evaluation of outcomes of regulatory decisions or the initiation of training programmes. In some situations, outside experts liberated from the immediate regulatory focus could provide additional insight into research and other scientific activities.

### 5.4. What kind of expertise does the PhVWP need ?

In general, additional expertise would be more helpful if it concerned domains of knowledge needed for the practice of pharmacovigilance than expertise in pharmacovigilance itself, which is already available at the level of PhVWP. Therefore, the PhVWP considers that there is a greater need for ad-hoc expertise than for the nomination of permanent experts who would attend all PhVWP meetings. On the other hand, by their involvement in PV issues, additional experts will acquire competence in risk management and will reinforce the pharmacovigilance expertise available in the PhVWP meeting they attend. It is also clear that additional experts would not replace national experts whom a member state would like to delegate to the meeting in order to present an assessment report or discuss decisions taken at the national level.

The additional expertise could be divided into four categories:

1. methodologists
  2. experts in drug-related sciences
  3. experts in clinical medicine
  4. other expertise.
- Methodologists These persons have an expertise in the methods used for assessing the efficacy and safety of drugs and for making drug regulatory decisions, both in the pre- and post authorisation phases. They may include statisticians, toxicologists, geneticists, physiologists, pharmaco-epidemiologists, public health specialists, communication specialists, etc. This list is not exhaustive.
  - Experts in drug-related sciences These experts have an in-depth knowledge of the subject matter, i.e. properties of toxic agents, active substances and medicinal products. They include experimental and clinical pharmacologists, who, increasingly, have specific areas of knowledge (e.g. neuro-pharmacologists, specialists in xenogenic products, pharmacokineticists/biopharmacists, specialists in innovative drugs, etc.
  - Experts in clinical medicine These experts are specialists in the areas of medicine of interest for a given dossier; they may be needed on an ad-hoc basis in the assessment of drug safety, e.g. cardiologists, nephrologists, etc.
  - Other experts There may be situations where other experts may be exceptionally consulted. For example, EUDRAVIGILANCE will generate a very large number of information on adverse reactions. It may be necessary at a later stage to seek advice from experts in Information sciences on how to organise and improve the data flow between national authorities, the EMEA and MAHs. Specialists of expert systems could also be needed to generate a tool for signal generation matching the WHO system.

### **5.5. How could additional experts be involved in the work of the PhVWP ?**

NCAAs should appoint their PhV expert - one person, or preferably two persons - to serve in the PhVWP on a long-term or permanent basis. This would ensure the opportunity for relevant competence to be provided and developed, and to enable time for preparations and continuity of service, and for collaboration with pre-authorisation staff.

The new organisation of the PhVWP from January 2003 may allow more flexibility for the involvement of additional experts. Some examples of situations where additional experts could be involved in the PhVWP are proposed below.

Example 1 During a PhVWP meeting, it is concluded that a dossier requires further in-depth assessment. In agreement with the Rapporteur/RMS/assessor, the PhVWP decides to nominate an expert for assessing the dossier and present his/her conclusions at the following meeting. The expert would be provided with the complete dossier, including confidential data. The choice of the expert will not be discussed during the plenary meeting but will be decided between the Chair of the PhVWP, the EMEA and the Rapporteur/RMS/assessor.

Example 2 In the course of evaluating a dossier (PSUR, referral, application dossier...), the assessor is of the opinion, in agreement with his/her own national experts, that it is necessary to seek additional expertise on a specific topic. For example, a new drug presents hepatic ADRs and the question is about which type of study could be conducted to assess the incidence and risk factors for these ADRs. The designation of the expert would be agreed with the EMEA and he/she would be provided with the necessary data. The expert would present his/her report at the PhVWP/CPMP meeting where this drug is discussed.

Example 3 An urgent safety issue concerning a centrally-authorized product occurs on a particular day. An urgent decision is needed for starting further investigations and issuing a press release. In agreement with the Rapporteur and the chairpersons of the PhVWP and CPMP, the EMEA immediately consults the relevant experts before taking any action. The whole issue is then presented at the following PhVWP/CPMP meetings in presence of these experts. In case this issue concerns a nationally-authorized product, the consultation of experts would be initiated by the RMS or national authority.

Example 4 While preparing the agenda for the next PhVWP meeting, the PhVWP chairperson and the EMEA secretariat realise that several topics concern the same class of drugs, the same pathology, the same pharmacological mechanism or the same method of investigation (e.g. results of several case-control studies will be discussed). The situation may also exist where a complex or technical dossier has been put on the agenda. In agreement with the EMEA, an expert in the subject concerned by this issue would be provided with the relevant documents and asked to participate to the PhVWP meeting.

Example 5 The PhVWP is informed through its chairperson or the EMEA secretariat that an expert group meeting on an important safety issue will be held (e.g. at the FDA or somewhere else). Due to time constraints or the complexity or technicality of this issue, it is not possible for a PhVWP member to participate to the meeting. In such case, the EMEA (in agreement with the Chair of the PhVWP and the Rapporteur/RMS/assessor) might appoint an expert to attend the meeting and report back to the PhVWP.

Additional experts mandated by the PhVWP may also participate to the CPMP, and vice-versa. According to the Rapporteur/RMS status, national PV experts to the PhVWP will also participate to the CPMP.

## **5.6. Practical arrangements**

In most situations, the need for additional experts will have to be decided rapidly and the experts will have to start their expertise with short notice. Therefore, it is obvious that, ideally, they need to be identified in advance. It is suggested to start by setting up a list of experts and update this list on a yearly basis. A "General Agreement" would also be signed by each expert and the EMEA. This General Agreement would specify the process for consultation and the financial arrangements. The expert would commit to perform its work within the specified timeframe and would sign the Declaration of Interest and other documents related to confidentiality of the data, etc..

The experts would be remunerated by the EMEA for each expertise, in addition to the reimbursement of travel and hotel costs. A scale of fees could be established by the EMEA according to factors such as speciality, amount of work, complexity of the dossier. For any expertise, the category of fees would be decided by the EMEA in agreement with the chairperson of the PhVWP.

The PhVWP proposes that training programs for experts in PhV could be provided by the EMEA for the new experts. It would seem worthwhile that such programs are made available also to the regular PhV experts of the NCAs

It is obvious that it will not be possible in the beginning to foresee the number of expertise and amount of work for the experts. These data will be gathered over the years with

## ***6. Components of a risk management strategy***

### **6.1. Introduction**

Pharmacovigilance is a public health endeavour which aims to analyse and manage the risks associated with medicinal products once marketed. The *analysis* phase includes the identification, quantification and evaluation (of social acceptability) of risks and the *management* phase includes the adoption and follow-up of administrative measures, the communication of risks and the implementation of prevention strategies. The analysis phase has to deal with *data* while the management phase has to deal with *actions*, and both phases are separated by *decisions*. Regulatory agencies have a major role to play in all these steps, but pharmacovigilance is so extensive field that regulatory agencies cannot accomplish it by themselves. There is a need to integrate further expertise in the process.

### **6.2. Risk detection**

#### *6.2.1. Limitations of the current system*

There are many situations where intensified risk detection is necessary in the early post-marketing phase, for example:

- clinical studies have shown the potential for a medicinal product to be associated with severe ADRs, but this risk has not been properly quantified or has been measured in selected patient population only. The benefit-risk profile for this drug need to be re-examined based on its use in clinical practice in a large number of patients;
- clinical studies have not shown any serious safety concerns for a drug, but its pharmacological properties, the toxicological data or the data from drugs of the same class give suspicion for a high potential for developing severe ADRs.

In these types of situations, regulators and MAHs need to re-assess the safety of the drug and take decisions soon after the start of the marketing phase. The current system of surveillance (including PSURs) is mainly based on spontaneous reporting whose advantages and limitations are well-known. Among the former are a coverage of all marketed prescription drugs from the day they are marketed, permitting the signalling of potential new reactions, and the relative low costs of the system. The main limitations include the lack of important clinical details, preventing an attribution of a causality relationship, and the underreporting. Underreporting is thought to be the result of three barriers related to the diagnosis, the attribution and the reporting itself.

Regulators may find it unsatisfactory to base their judgements on a system on which they have a limited control and whose effectiveness may be influenced by a large number of factors, including direct intervention from MAHs to prescribers. For certain safety issues, for certain medicinal products, or for certain populations, spontaneous reporting may not be sensitive enough and needs to be complemented with other permanent sources of information.

## 6.2.2. Proposals for improving risk detection

### Planning of early phase post-marketing surveillance

At some suitable phase of the authorisation process, e.g. day 70, anticipated safety problems of a new product - on the basis of data from e.g. RCTs, on its mechanism of action or on certain biological properties – there is need for an early phase post marketing vigilance plan to be jointly evaluated. Commitments of the MAH to perform safety follow-up studies or for initiatives by the NCA to perform intensive monitoring studies are examples of measures that can improve the efficiency of PhV. The organisation for such early collaboration needs to be put in place at the NCA and EMEA levels. The CPMP could define domains where additional data collection is necessary, with commitments from the MAH to perform studies (e.g. risk estimation, identification of at risk population). Focus should be given to both short-term and long-term studies. Timetable, study questions to be and study protocols should be approved before authorisation is granted. The CPMP could also request more frequent PSUR submission, with simplified PSUR format and shortened delays for the submission/review procedures.

### Spontaneous ADR reporting

Spontaneous ADR reporting should remain one of the cornerstones of a comprehensive safety monitoring programme. In most EU countries, suspected ADRs are reported to the national drug regulatory authority, where they are reviewed and entered into a computerised database to facilitate future aggregate analyses and report retrieval. Currently, signal detection is performed by two main activities:

- systematic review of spontaneous ADR reports, for the purposes of identifying unrecognised potential hazards and gaining new information about established ADRs
- regular and systematic review of the database.

Improvement of the spontaneous system needs a multidisciplinary approach addressing different steps of the reporting process.

- ***Health professionals should be encouraged to report.*** Several methods have been used to encourage the reporting by health professionals. The choice of methods should be made at the national level, as their success is partly dependant from the cultural environment. Secured electronic transmission of ADRs by health professionals would facilitate the administrative tasks of filling and mailing a case report.

The black triangle system applied in the UK for certain classes of products is a useful tool that could be generalised to other European countries. The duration of the system for any single product should be standardised and amended as needed at the time of authorisation.

Other methods to encourage reporting are the use of spontaneous reporting for providing feed-back information and dialogue with reporters, or as a basis for training sessions.

- ***Reporting in special situations*** Intensive monitoring may be needed for some categories of drugs or some settings. For example, a specific system for the detection and reporting ADRs in hospital settings could be put in place, especially for drugs newly introduced in hospitals. Such intensive monitoring may require an amendment of the current legislation at national and/or European levels. Another special situation where reporting should be

reinforced concerns the collection and use of data on maternal medication use during pregnancy, especially in European-wide birth defect registries.

- ***Improving the quality, completeness and harmonisation of the reporting forms.*** Spontaneous reporting forms could be harmonised across Europe in order to harmonise the data collection.
- ***Improving tools for signal detection*** The Eudravigilance database and data-processing network which has been put in operation on 5 December 2001 should facilitate the exchange of Individual Case safety Reports (ICSRs). It is considered by the PhVWP a potentially very important resource for improved signal detection. Its full potential requires that tools for data transfer, filing and mining are of adequate performance and quality. Further, the responsibility for signal detection in the data-base needs to be clearly defined, whether it should be up to special staff of the EMEA, assessors at the responsible NCAs, or a collaborative effort. The PhVWP proposes that the database would be screened, with the help of sophisticated data mining tools. Signals arisen from Eudravigilance would be discussed in a specific part of the PhVWP meetings.

#### Post-marketing studies

Post-marketing studies for intensive and early monitoring could substantially help to quickly characterise the risk and effect profiles of novel drugs, identified in the pre-authorisation phase to have a particular need for safety follow-up. In order to gain time in protocol development, a categorisation of different types of PMS studies (cohort, case-control, etc.) could be developed. Each type would have its own objectives, methodological requirements, standard protocol model and standard reporting model. NCAs should also explore the possibility to perform such short-term postmarketing studies in collaboration with relevant clinical and academic departments, and preferably independently of the MAH (see section 3.4). Single MSs may contribute useful information from national data; an efficient strategy would be to establish a network of academic units in different MSs. Rapporteur MSs would have the lead responsibility for the particular product. Such system would benefit from EU funding.

#### Registries and follow-up programmes

Based on recent experiences (sertindole, cisapride, tolcapone...), the methodological framework for registries or follow-up programmes of patients treated with a medicinal product should be developed in order to gain time in the development of protocols, registration documents, follow-up procedures, ADR notification procedures, etc... Registries may address specific diseases frequently associated with drugs ( e.g. haematological disorders, severe hepatic and skin disorders, congenital malformations. ..). Follow-up programs may concern certain populations (e.g. pregnant), or populations exposed to special medicinal products (e.g. biologicals, xenogeneic cellular products).

#### Drug utilisation data

In the initial phase of marketing (and thereafter for each renewal), the MAH should collect data on utilisation patterns of the drug and deviations from authorisation conditions. These data could include the number of treated patients, daily prescribed doses, duration, indications, co-medications... Consideration should be given to a more extensive use of prescription databases. These exist in most countries, the majority of them being based on the coding of prescriptions at the pharmacy level (see section 7.2.5). Attempts should be made to

establish links across European countries in order to obtain a more global view of drug utilisation patterns in Europe. Specific physician-based drug utilisation surveys may also be useful.

#### Need for cooperative agreements

As agencies do not normally have the capability to set up by themselves. post-marketing studies, registries or follow-up programs, the most effective way to proceed is to formalise cooperative agreements with professionals from the academia, hospital settings or scientific societies who may run such registries or programs. This will assure the prompt transmission of important information, the use of the registry/program for signal :amplification/hypothesis-testing and, in addition, a first-hand evaluation of the problem observed. An enquiry all over the European Union to know the existing registries or follow-up programs would be the first step to be taken. Thereafter, the Pharmacovigilance Working Party, helped by national experts, would elaborate a listing of registries and follow-up programs that should be either supported or implemented. Normally, one national agency should take the lead for each registry or program, meaning that such agency would run the registry/program or would be the contact point for the external experts running the registry/program. The funding would be provided by national agencies/EMA.

### **6.3. Risk quantification**

Risk quantification normally requires formal epidemiological studies to be performed, in order to provide valid and precise measures of frequency and association. One cost efficient way would be to monitor intensely during a few initial years the patients who are prescribed the particular drug within a defined clinical setting. Such post-marketing intensive monitoring studies for selected new drugs should ideally be performed by academic departments in collaboration with pharmacovigilance units of the NCAs to produce optimally reliable scientific result. However, this system is difficult to be used for older products and cannot provide results within short timeframes, unless there exist efficient and validated data sources.

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. For databases commonly used, the population characteristics should be compared to characteristics of the populations in other European countries, in order to assess to which extent results from such databases can be inferred to other countries.

Although there are a number of good databases in the European Union, they are still scarce. National agencies must support (or lead) such important developments. Formal agreements with the institutions running the databases (e.g. GPRD, IMS) will be essential in the near future, in order to assure access to the raw data and/or with the epidemiologic teams with experience in conducting studies using such databases. Such agreements (including funding) should be made by national agencies and/or the EMA. The custom of yielding the MAHs the whole responsibility to carry out such studies should be revisited.

### **6.4. Risk assessment**



The safety profile of a product is assessed based on a pooled analysis of all human safety data, including, where appropriate, preclinical data. Risk assessment requires the ability to put in perspective the safety profile of the drug taking into account the safety profile of alternative drugs, to identify the data needed to properly evaluate the risk depending on the level of future exposure and the severity of the treated disease, and to identify the strategy for monitoring the adverse effects and to define the appropriate PhV actions. Risk assessment is the area where external expertise has been most often used by agencies until now. At this level also, collaboration with relevant university departments should be encouraged. One reason would be to give an opportunity to the PhV responsible person(s) to receive scientific training, to exchange research data and to increase the competence at the level of the NCA. Further, a network of university departments can provide the necessary infrastructure and competence to perform and analyse safety follow-up studies.

At the European level, PhV and academic experts should participate at the CPMP and its various working parties.

## **6.5. Risk minimisation**

This phase includes the adoption and follow-up of administrative measures, the communication of risks and the implementation of prevention strategies. The need for strengthening of PhV work during the pre-authorisation phase, rationale for risk management plans and for early phase post marketing vigilance were discussed above (see sections 3.1 and 4.3).

Difficulties experienced by Regulatory Authorities to implement decisions and follow-up on recommendations in the post-authorisation phase have also been delineated above, and proposals have been made both at the national and the European level (see sections 3.2 and 4.4). It needs to be emphasised that amendments of the pharmaceutical legislation is a prerequisite for the effective enforcement of different types of post-authorisation commitments.

Administrative measures adopted to minimise risk should be followed-up to evaluate their impact. In order to do so, access to drug utilisation data sources should be assured. If they are not available, consideration should be made to the setting up of national networks (e.g. community pharmacies) to obtain such information (see section 7.2). National agencies should make agreements with those institutions/experts that may provide the information and the expertise. Needless to say that the evaluation of measures impact should necessarily be done in every Member State, because the results obtained in one Member State may not be valid for the others.

## **6.6. Risk communication**

### *6.6.1 Introduction*

Communication is defined as “*the exchange of information between individuals, e.g. by means of speaking, writing or using a common system of signs or behaviour.*”

Evaluation of safety information relating to medicines results in an evaluation/outcome which needs to be communicated as appropriate, in a systematic way to the relevant parties e.g. to other agency departments and expert groups, MAHs, EMEA, other Regulatory Authorities, WHO, healthcare professionals, patient groups, the general public and the media. The provision of communications relating to the safety of medicines has the potential to significantly impact on the general public, particularly if the safety issue concerned has a broad public health interest, e.g. an issue related to the use of childhood vaccines.

In order to meet the needs of all potential interested parties, as described in “*The Erice Declaration*”, Competent Authorities should work to develop methods of openness and transparency to foster a climate of trust and mutual respect. These methods should be consistent with any Freedom of Information legislation in place and at the same time respect the need to protect patient confidentiality, as required by the Privacy Directive.

#### *6.6.2. Principles of communication*

Taking into account the definition of communication above, Competent Authorities should consider the following principles in the preparation of all types of communications.

- Competent Authorities should increase the visibility of their reporting systems and make information about their procedures available
- Communications should be clear, concise, consistent and comprehensive.
- Communications should be targeted to take account of the recipients needs (i.e. health care professionals, patient groups, consumer groups and the general public).
- Communications should conform to the requirements of the Privacy Directive and any Freedom of Information legislation in place
- Standard procedures for communication should be developed (i.e. contact points for further information, standard statements regarding advice to patients etc.)
- Competent Authorities should provide details of relevant ADR reports to Marketing Authorisation Holders, the EMEA and WHO in keeping with legislative requirements.
- Competent Authorities should liaise with other agencies (EMEA/WHO/FDA/MAHs etc.), to share information on evaluation of safety issues.
- Competent Authorities should fully respect embargos agreed with other agencies/MAHs etc. for distribution of information.
- Competent Authorities should establish an internal review procedure for all communications issued, to include the information/public relations officer.

The overriding principle of all communications should be to ensure that the right message is delivered to the right person (s) at the right time.

Provision of information about the safety of medicines must be considered as a public health responsibility and an integral part of overall health care systems. To this end it is essential that adequate resources are made available to meet the goal of timely and effective communications.

#### *6.6.3. Personnel*

Within individual Competent Authorities, it is likely that many staff members will provide information to many sources, from members of the general public, special interest groups,

media sources, pharmaceutical companies etc. It is important therefore, that Competent Authorities develop a strategy, known to all staff members to ensure that all queries are dealt with appropriately. This is particularly important when “crisis” issues are being managed.

While resources will vary from one Competent Authority to another, appointment of a specific Information/Public Relations Officer should be considered as an important link in the communication chain. Such a person has a unique opportunity to work with individuals within and outside the Competent Authority, to ensure that all queries are dealt with by the appropriate personnel, that responses provided are consistent with information previously provided, to act as a reservoir for all information issued by the Competent Authority and, if necessary or considered appropriate, to speak on behalf of the Competent Authority.

#### *6.6.4. Data sources*

As mentioned above, information about the safety of medicines is increasingly available from a wide range of sources. This includes official information such as summaries of product characteristics (SPCs) and Patient Information Leaflets (PILs), national drug safety bulletins, press releases, newspaper and magazine articles, internet web-site information, radio and television documentaries and soap operas. Competent Authorities need to monitor all such sources of information, to liaise with relevant personnel, including the information/public relations officer to determine if and when comments, clarifications etc. should be issued.

#### *6.6.5. Routine communications*

At each stage of the pharmacovigilance process, information is communicated. This starts with receipt of a suspected ADR report, which prompts an initial review and evaluation of the case. This review results in communication within the Competent Authority by relevant staff, generation of an acknowledgement letter and/or request for further information from the original reporter. Further communication documents are then generated in the form of report(s) for the MAH, EMEA and WHO, as appropriate. Individual/aggregated reports may also be communicated to others through assessment reports, PSURs etc. Anonymised information may be subject to comment in "Dear Healthcare Professional" letters and/or national drug bulletins and may give rise to regulatory action. Competent authorities should establish standard procedures for the management of all stages of the pharmacovigilance process, to ensure consistency of approach, which should be reviewed regularly to take account of any changes necessary.

#### *6.6.6. Crisis communications*

The challenge of providing effective information when there is an apparent crisis associated with the safety of a medicine is significant. Information may be rapidly evolving, continually affecting and altering assessment of the issue. Furthermore, assessment of the issue may be hampered by incomplete or inconclusive data. It is essential therefore, that liaison with the relevant partners as outlined above occurs and, if possible, that all staff members are fully briefed to deal with the issue and all queries arising from it, to ensure consistency of information provided.

It is important to remember too, that in a crisis situation, communications may be issued by several interested parties, Competent Authorities, the EMEA, pharmaceutical companies, patient groups, consumer groups etc.

While assessment of an issue may change rapidly, there is a need to avoid information overload and to provide carefully balanced information, which, if necessary, reflects any doubts or uncertainties relating to incomplete/inconclusive data or findings.

Such issues often give rise to a disproportionate amount of media interest, particularly if there is a perception that the issue impacts on general public health issues, increasing the challenge of putting safety data in context and comparing the risks with other known and well recognised risks.

#### *6.6.7. Targeting communications*

As mentioned above, it is essential that communications are targeted to meet the relevant groups needs. Healthcare professionals may need specific advice on revised prescribing recommendations, alternative treatments/dosing information, investigations to be undertaken etc., while patients/consumers may need advice regarding discontinuation of treatment, when to return to their doctor or pharmacist etc. Patient groups, who will already be familiar with issues relating to their condition and treatment will have a different level of understanding to that of the general public.

#### *6.6.8. Timing of communications*

As well as ensuring that communications are clear, comprehensive and targeted, they should also be provided in a timely fashion (i.e. when the issue is topical), and in as far as possible, should coincide and be consistent with other information provided e.g. by other agencies, the MA holder etc. To this end, any timetables/embargos agreed relating to release of information should be respected. Competent Authorities should develop systems to facilitate prompt distribution of information to healthcare professionals, patient groups, media contacts etc.

To meet this need, it is essential that Competent Authorities liaise closely with Marketing Authorisation Holders and adhere to the principles described in the Note for Guidance on the Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in Human Pharmacovigilance.

#### *6.6.9. Risk perception*

Serious ADRs are relatively rare, particularly compared with other potential adverse events such as road traffic accidents. However, because road traffic accidents are considered a well established risk and possibly also because individuals feel a greater degree of control over driving or travelling on the roads, there appears to be a greater acceptance of such a risk. It is therefore important for competent authorities to participate in education of healthcare professionals, the general public and the media to encourage understanding of the benefits and risks of medicines and to promote more active participation by the public in putting information regarding the risks of medicines in context.

The media should be encouraged to provide balanced reporting and avoid sensationalising stories which may over emphasise benefits on one occasion and over emphasise the risks on the next. Competent authorities should strive to work with patient groups, academic

institutions and general public education programmes to investigate the level of understanding of the benefits and risks of medicines, to correct inaccuracies and misunderstandings through improved educational programmes and to carry out market testing of important communication documents.

#### *6.6.10. Evaluation of impact/effectiveness of communication*

Up to now the impact of communications provided by Competent Authorities has rarely and only informally been evaluated, in terms of whether the information provided has been received, clearly understood and considered helpful by the recipients. Competent Authorities should take steps to develop such evaluation procedures by encouraging links with relevant healthcare professional organisations, patient and consumer groups and the media. Such links would facilitate appropriate input and enhance the development of trust between the Competent Authorities and the relevant groups.

In addition, Competent Authorities should develop a pro-active approach to the provision of information to ensure that not only messages relating to adverse effects of medicines are communicated and to highlight awareness of the overall activities of the Competent Authorities.

In compiling information for dissemination to different groups, it is important to remember the inherent limits with pharmacovigilance data, (i.e. lack of denominator data, limited data quality etc.) In addition, health care professionals and consumers may be unaware of the limits of pre-marketing drug safety assessment.

Competent Authorities in conjunction with relevant bodies (academic and educational institutions, consumer and professional bodies), need to develop and enhance targeted educational programmes to include information on the pre and post marketing assessment of drug safety. Such programmes should highlight the limits of available data, e.g. lack of denominator data, variability of report quality, under reporting, the limits of pre-marketing data etc.

Public health education programmes should include information about ADR monitoring programmes and encourage consumer and patients to discuss suspected ADRs with health care professionals.

#### *6.6.11. Reference*

The Erice Declaration on Communicating Drug Safety Information. *Prescrire Int*, 1998; **(38)**: 191

## ***7. Audit of decision making and monitoring of outcomes***

### **7.1. Audit of the decision-making process**

#### *7.1.1. Introduction.*

According to the community legislation every MS should have a pharmacovigilance system in place, capable of performing the different tasks associated with the post-marketing surveillance of drugs.

Pharmacovigilance is fundamental for the continued safe use of drugs. Every effort must be done to establish "best practice". It is important to gain knowledge of obstacles to be overcome and to (be able to) measure the effectiveness / impact (over-all and for different steps) of regulatory actions. Standards should be defined and agreed, and the performance should be measured. The experiences gained during the process and throughout the years should be evaluated with the aim of improving pharmacovigilance in areas where activities are yet insufficient. Developments – whether strictly medical or technological – should be taken on board.

Below the different major steps in pharmacovigilance is briefly described, together with proposals / examples where to and how audit could be applied / performed. The main focus is on the spontaneous reporting system, as the individual and spontaneously collected case reports still are the main source of information. The management of Periodic Safety Update Reports and data collected from the literature and post-marketing safety studies should, however, also be covered by the audit, as such information also is used to an increased extent.

#### *7.1.2. Data management.*

##### Steps.

Data management includes collection of data, registration, retrieval, assessment, analysis and interpretation, followed by risk/benefit evaluation and signal generation.

##### Sources of information – spontaneous reports.

The main source of information is the spontaneous reports submitted by health care professionals. The spontaneous reporting system is advantageous as it covers different types of ADRs, including interactions, pharmaceutical defects, overdose and abuse / misuse. Further more it is a rapid and cheap way of communication. On the other hand there are certain limitations. Physicians may not recognise ADRs. Underreporting is prevalent, to a variable extent for different drugs. Reporting bias may occur. Data are heterogeneous and to a great extent unproven. The single reports represent only signals and the huge amount of data makes it difficult to get an overview.

##### Reporting characteristics.

Due to existing underreporting it is mandatory for the regulatory authority to try to improve the reporting rate. Frequent drug- and/or ADR-specific analyses in e.g. hospital settings and /

or among general practitioners should be performed, in order to establish the degree of underreporting (expected ADRs quantitatively and qualitatively compared to actually received). Regulatory authorities should also ensure that relevant new safety information is forwarded to the relevant parties. Individual feedback to the reporters - with information on the result of the causality assessment, previous experience and consequences - should be mandatory. By these activities the regulatory authorities make health care professionals aware of their own responsibility in this area.

General performance criteria should be provided regularly. These include the reporting rate (e.g. number of reports/number of inhabitants/year), reporting distribution (proportion of physicians, reporter characteristics), reporting quality (completeness of information), reporting efficiency (proportion of relevant case reports). These data should be made public to the health care professionals in order to increase their awareness of underreporting.

### Report processing.

In processing the reports submitted to the regulatory authority it is important to ensure, that the quality of the data is acceptable. Missing data with important impact on the causality assessment should be requested from the reporter. When registering the data in the database care should be taken that all relevant data are incorporated in the register. Quality control systems should be in place which hinder further processing if data are missing. In the retrieval process several database searches should be performed, using different search criteria, to ensure that the result that the outcome is complete and valid.

The time period which elapses from the receipt of the report at the regulatory authority until the

- preliminary registration in the database
- medical assessment
- conclusion
- final registration in the database
- feed-back to the reporter

should be measured, and standards should be defined / agreed, followed by measurement of the performance.

The quality of the assessment of the spontaneous reports should be verified. The degree of consistency in the result of causality assessments among different assessors should be established, in collaboration with the national advisory committee.

Information from literature, other registers, pharmaco-epidemiological studies and post-marketing safety studies should be utilised. Confounding factors should be identified. The practice in data assessment at different regulatory authorities should be compared. Standards should be defined / agreed, followed by measurement of the performance.

#### *7.1.3. Communication.*

When the need for a regulatory action has been identified, the communication strategy should be settled. Information should be provided to health care professionals and the general public.

The appropriate kind of information (DDL, communications in national / international drug bulletins, press releases etc.), target groups and media should be considered and identified.

Questions to be asked are:

- Did the message get through to the relevant people?
- Level of compliance of prescribers and patients?
- Level of future ADRs reported?

## 7.2. Monitoring outcomes of regulatory decisions

### 7.2.1. Objectives

The effectiveness of regulatory decisions is a key element for the ability of pharmacovigilance systems to protect public health. Measures taken to improve the safe use of a drug need to be rapidly assessed and corrected as necessary. However, spontaneous reporting systems may not be adequate to provide prompt and valid information on changes in the utilisation patterns and safety profile of a drug. In order to increase the effectiveness of such measures, regulatory authorities should establish a system to collect and evaluate data allowing to:

- assess the effectiveness of communication to health professionals and to patients, and identify barriers to it;
- evaluate the level of compliance of prescribers and patients to recommendations;
- assess the impact of regulatory decisions on morbidity/mortality;
- identify at an early stage implementation failures and decide additional actions.

The system should also be designed as an on-going learning process on how to deal effectively with drug safety hazards, e.g. how to improve communication strategies. The knowledge gained through a critical examination of previous experience should normally be translated to a change of practice and procedures.

### 7.2.2. Final and intermediate outcomes

A regulatory action can be considered as an intervention, the outcomes of which may be intermediate and final. The **intermediate outcome** is the effect of the decision on the pattern of drug usage or prescription. At a first level, differences in sale figures may be useful to evaluate how drug consumption was influenced. Detailed data may be needed for a more accurate assessment. For example, one may wish to investigate if the addition of a new contra-indication into the SPC actually leads to a restriction of drug use in the patient group concerned. It could also be of interest to know if two drugs are still prescribed concomitantly after an interaction has been recognised, mentioned into the summary of product characteristics and communicated to health professionals. An evaluation of an intermediate outcome is particularly useful in situations where a hazard has a low risk of occurrence or manifests itself after a long delay. Such evaluation requires two assumptions: 1) there is a known relationship between the utilisation pattern of drug and its safety profile; 2) a modification of the utilisation pattern is known to improve the safety of the drug. The validity of these assumptions should be assessed in each case. An evaluation of intermediate



outcomes does not require knowledge of the patients' clinical outcomes. Its implementation may therefore be less resource-consuming.

The **final outcome** represents the effect of the decision on morbidity and mortality. For example, one could assess the incidence of new cases of an ADR after the dosage of a suspected drug have been reduced or its contra-indications strengthened.

The evaluation of final outcomes may be performed at the level of the population or at the level of the patients. At the population level, it may be based on a comparison of the incidence of an ADR before and after a regulatory measure has been implemented. The validity of such comparison requires the assumption that other conditions associated to the occurrence of the ADR have not changed during the same period. Incidence data may be based on registries, databases or specific surveys, or, in some circumstances, be estimated from the reporting rate to the spontaneous reporting system.

An evaluation at the patients' level provides stronger estimates of association, but requires data on clinical outcomes and follow-up of treated patients. It also requires data on determinants of the outcome, such as indication, underlying morbidity, co-medication, drug usage, etc... An assessment of final outcomes will therefore be performed in a context of patient-based epidemiological studies based on specific data collection or record linkage database such as GPRD. In some circumstances where there is a high background event rate, an analysis of case reports may compare the proportion of events associated with the suspected drug before and after the regulatory measure has been taken.

The evaluation of final outcomes suffers from the same difficulties as those met in carrying-out full-blown epidemiological studies. Among these difficulties are the requirement of extensive data collection where the needed information is not included in existing database, the great caution to be exercised in order to minimise the presence of methodological biases distorting the result of the evaluation, and the high cost associated with data collection.

Both intermediate and final outcomes should be assessed with measurable indicators. These indicators should preferably be relative measures comparing the pre- and post-intervention situations. Ideally, they should be interpreted in comparison with expected effects.

### *7.2.3. Type of measures amenable to evaluation*

Regulatory measures in the field of pharmacovigilance aim to protect public health by improving the safety of drug use. Failure to achieve this objective may have severe untoward consequences for the patients. Additional conditions where the drug is contra-indicated or not recommended, additional precautions for use, advice on dosage and mode of administration are aspects of drug use which prescribers, pharmacists and patients should be accurately and rapidly informed about. Failure of communication in these regards may be a threat for patients' health. When performing an audit, the priority should therefore be given to evaluating the effectiveness of the regulatory measures in situations where severe undesirable effects may result from inappropriate drug use.

The design of the evaluation may vary according to the measure that needs to be audited. In case overt clinical conditions or concomitant medications are included among contra-indications or require special warnings for the use of the drug (for example, active thrombophlebitis), a patient-based survey will allow to estimate the proportion of patients prescribed with the drug who have one of the conditions or take one of the contra-indicated medication. Such an evaluation will not be possible when a contra-indication consists in the

result of a test (such as, for example, a creatinine clearance <30 mL/min) or previous undesirable effects to another drug, which the patient may not be aware about..

Some measures are also less amenable to evaluation because of the legal implications of a prescription outside the terms of the SPC. For example, the compliance to a restriction of indications may not be accurately assessed through the patient or the prescriber.

Intermediate steps between the implementation of a regulatory decision and an intermediate or final outcome should also be investigated. An important aspect in this evaluation is the effectiveness of the communication to health professionals and patients through Drug Information Bulletins, Press Release, Dear Doctor Letter or other channels. Questions such as "Have prescribers/patients been aware of the communication?", "How have they been informed ?", "How much time has elapsed between the issuance and the receipt of the information?", "How has been the message understood and interpreted ?" and "What was the main message retained" are examples of issues to be evaluated.

#### *7.2.4. At which level of the health system should the evaluation be carried out?*

Different options may be envisaged according the regulatory measure whose effectiveness needs to be evaluated. Physicians ' awareness of a drug-related issues is important as it influences their prescribing practice, but the information retained by patients regarding e.g. warnings and dosage recommendations may also matter. These views may not be contradictory, as different decisions may require different levels of evaluation.

For example, a patient may not be aware of whether he presents or not a medical contra-indication for a medicinal product, but he may know if he takes a concomitant drug that is contra-indicated.

#### *7.2.5. Source of data*

Several sources of information may be used to collect data on the effectiveness of regulatory decisions. These sources of information should be rapidly accessible to Regulatory Authorities.

Different sources of information may be needed to answer different questions. Each of them has strengths and weaknesses in terms of accessibility, timeliness, extent of information provided and resource use. Examples of sources of information with their strengths and weaknesses are provided in the Annex.

Regulatory authorities should identify sources of information which can be rapidly accessed and used. A minimum set of design specifications to be used in survey protocols should be established in order to achieve standardisation and comparability of results.

ANNEX: Source of data for monitoring outcomes

### **1. Prescription database**

Prescription database exist in most countries, and the majority of them are based on the coding of prescriptions at the pharmacy level. The information collected may vary from country to country, but the minimum information generally includes individual drug characteristics, such as dosage, package, strength and cost. Information on age, sex and other demographic information may also be available in some settings. In some countries, a record linkage system links prescription data and data on clinical

outcomes.

## **2. Pharmacy-based utilisation surveys**

Pharmacy-based utilisation surveys may be performed through questionnaires provided to patients by pharmacists, filled in by the patient at the pharmacy, and returned by pharmacists to study staff or sent back directly by the patient. Research groups of pharmacists exist in most countries. They are often organised locally on an ad-hoc basis and may participate in utilisation studies depending on their interest. Academic groups or research groups organised by professional associations also exist. Utilisation studies are also performed by Marketing Authorisation Holders. They can be a valuable source of information but their results should be used after a careful consideration of their objectives and design.

## **3. Physician-based utilisation studies**

In many countries, networks of general practitioners interested in research activities have been established by academic Departments of General Practice or professional associations of general practitioners. These groups are generally interested to participate in utilisation studies, depending on the topic of these studies and their relevance for their practice (e.g. use of antimicrobials).

Physician-based utilisation studies may take several forms, for example the provision of prescription pads with auto-copying paper for registration of consecutive prescriptions. In more developed epidemiological studies, physician-based studies may also provide follow-up information on clinical outcomes. A special application of such studies is the Prescription Event Monitoring system in the United-Kingdom, where encashed prescriptions are subsequently followed-up at GP level after a period of 6 months to identify adverse events. Physician-based studies are most easy to perform when all data are computerised and collated in a single database, such as in GPRD. Many physician-based utilisation-based have been carried-out with a sponsorship from the pharmaceutical industry. Use of these studies for regulatory purposes should be preceded by a careful consideration of their objectives and methodological aspects. Results of unpublished studies as well as published studies should be used.

### **2.4. Analysis of ADR reports**

This analysis may provide a descriptive analysis of information included in ADR reports before and after regulatory decisions have been made. For an analysis of prescribers' compliance to recommendations, all ADRs for one drug must be analysed (not only ADRs which triggered the action); for identification of risk factors for a defined reaction, only those reports of the reaction should be considered.

In practice, this kind of evaluation is feasible if all the necessary information is coded and included in the ADR database. Information received from member states shows that the role of interactions and dosage could be possibly evaluated, but this would not be possible for other measures, such as contra-indications due to co-morbidity, as not all variables are coded.

A limitation of analysing ADRs is the likelihood of reporting biases, which is inherent to this source of data.

## ***8. Conclusions***

In the view of the PhVWP, there is a great potential for improvement of PhV to the benefit of public health. The manifold detailed strategies will need much work to be developed and realised, both at the levels of MS and of the EMEA. The PhVWP is prepared to contribute in all relevant aspects of the forthcoming work.