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Guideline on Risk Management Systems for Medicinal Products for Human Use

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1. INTRODUCTION (BACKGROUND)

It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited. This is due to many factors including the small numbers of subjects in clinical trials, restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, relatively short duration of exposure and the statistical problems associated with looking at multiple outcomes.

A medicine is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk is judged positive for the target population. However, not all actual or potential risks may have been identified when an initial authorisation is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the population as a whole.

Over the last few decades many important pharmacovigilance issues have been identified through spontaneous reporting of adverse drug reactions. At the same time, consideration has been given to ways in which the current reporting systems might be augmented and strengthened. A strong contender is that planning of pharmacovigilance activities might be improved if it were more closely based on product specific issues identified from pre- or post-authorisation data and from pharmacological principles. Such planning would also guide the use of routine electronically collected data within health services to provide rapid investigation of predicted or emerging safety concerns. This new proactive approach has now been recognised in the European Pharmaceutical Legislation including a specific reference to risk management.

The management of a single risk consists of four steps, risk detection, risk assessment, risk minimisation and risk communication. However, a typical individual medicinal product will have multiple risks attached to it and individual risks will vary in terms of severity, and individual patient and public health impact. Therefore, the concept of risk management must also consider the combination of information on multiple risks with the aim of ensuring that the benefits exceed the risks by the greatest possible margin both for the individual patient and at the population level.

Recently introduced legislation discusses the use of a risk management system but it does not define it. A risk management system is defined in this guideline as *a set of pharmacovigilance activities and interventions designed to proactively identify, characterise and prevent or minimise risks relating to medicinal products, including risk communication and the assessment of the effectiveness of risk minimisation interventions.*

This guideline aims to provide guidance on how Marketing Authorisation Holders (MAHs) and Applicants (MAAs) should meet the requirements for a description of a risk management system that they will introduce for an individual medicinal product or a series of medicinal products in line with new Community legislation. The guideline also describes how such a risk management system can be presented to Competent Authorities in the form of a Risk Management Plan.

Risk management is a continuing process throughout the life-cycle of a medicinal product. However, the tools used for risk management may be changed by technical, scientific and legislative developments, as well as by the information available, the perceived risks and their estimated public health impact and where a product is in its lifecycle. All these factors should be taken into account when formulating risk management plans in the EU.

2. SCOPE

EU legislation now requires MAA/MAHs to provide Competent Authorities with a description of pharmacovigilance and risk management systems.

The requirements and format for the description of a pharmacovigilance system are covered in "The guideline on monitoring of compliance with Pharmacovigilance regulatory obligations and Pharmacovigilance inspections for Centrally Authorised Products" and should be submitted in accordance with this guideline.

The present guideline provides guidance to Marketing Authorisation Applicants (MAAs) and Marketing Authorisation Holders (MAHs) in the European Union on how to meet the requirements for a 'detailed description of the risk management system' (section 4.1) and the circumstances when it is appropriate (sections 4.3 and 4.13) to provide it. It is applicable to products in both the pre-authorisation and post-authorisation phases of either the centralised or mutual recognition procedures. It incorporates the concepts of the International Conference on Harmonisation (ICH) E2E Guideline.

3. LEGAL BASIS

Article 6 of Regulation (EC) No. 726/2004 and Article 8 of Directive 2001/83/EC lay down the particulars and documents to be included in an application for the authorisation of a medicinal product for human use. More specifically and for the purpose of this guideline it requires in accordance with Article 8 (3)(ia) of Directive 2001/83/EC as amended the inclusion of *"a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce."* This provision forms the legal basis for this guideline.

In the context of centrally authorised products Article 9 (4) of Regulation (EC) No 726/2004 requires for a favourable opinion that the following shall be attached to the Opinion:

b) "details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including conditions under which the medicinal product may be made available to the patients, in accordance with the criteria in Title VI of Directive 2001/83/EC"

c) "details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product"

In addition to Article 9 (4) (c) above, Article 127 a) of Directive 2001/83/EC, as amended states that *"When a medicinal product is to be authorised in accordance with Regulation (EC) 726/2004 and the Scientific Committee in its opinion refers to recommended conditions or restrictions with regard to the safe and effective use of the medicinal product […], a decision addressed to the Member States shall be adopted in accordance with the procedure provided for in Article 33 and 34 of the Directive, for the implementation of those conditions or restrictions"*

The legislation provides for additional information to be requested from MAHs.

Article 23 of Regulation EC 726/2004 states *[…] That qualified person shall reside in the Community and shall be responsible for the following:*

c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the risks and benefits of a medicinal product is answered fully and promptly, including the provision of information regarding the volume of sales or prescriptions for the medicinal product concerned […]

d) providing the competent authorities with any other information relevant to the evaluation of the risks and benefits of a medicinal product particularly information concerning post-authorisation safety studies.

Similarly, for nationally authorised products, Article 103 (c) of Directive 2001/EC/83 states *[...] That qualified person shall reside in the Community and shall be responsible for the following:*

c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned;

d) the provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorization safety studies.

Article 26 of Regulation EC 726/2004 *[...] for a period of five years following the initial placing on the market in the Community, the Agency may request that the Marketing Authorisation Holder arrange for specific pharmacovigilance data to be collected from targeted groups of patients. [...]*

4. RISK MANAGEMENT DESCRIPTION AND THE REQUIREMENTS FOR APPLICANTS AND MARKETING AUTHORISATION HOLDERS

The detailed description of a risk management system should be provided in the situations described in section 4.3, in the form of an EU Risk Management Plan (EU-RMP). It is strongly recommended that discussions with the Competent Authorities on the need for and content of an RMP should take place in advance of submission.

4.1 Description of the risk management system.

A risk management system is a set of pharmacovigilance activities and interventions designed to proactively identify, characterise, prevent or minimise risks relating to medicinal products, including risk communication and the assessment of the effectiveness of risk minimisation interventions. The legislation requires that a description of the risk management system should be submitted when appropriate. This requirement can be met by the submission of an EU risk management plan (EU-RMP) in the circumstances detailed in sections 4.3 and 4.13.

The aim of a risk management system is to ensure that the benefits of a particular medicine (or a series of medicines) exceed the risks by the greatest achievable margin for the individual patient and for the population as a whole. This can be done either by increasing the benefits or by reducing the risks but, by its definition, risk management focuses upon the risk reduction approach. Nevertheless, whenever possible, increases in benefits should also be considered and the characteristics of patients most likely to benefit from treatment investigated.

4.2 EU Risk Management Plan (EU-RMP)

The EU-RMP contains 2 parts:

Part I

- A Safety Specification
- A Pharmacovigilance Plan, and

Part II

- An evaluation of the need for risk minimisation measures, and if there is such a need:
- A risk minimisation plan

Part I of the EU-RMP incorporates the concepts of ICH-E2E regarding the safety profile of the medicinal product at the point in time of its life cycle. Sections 4.5 and 4.6 of this guideline include relevant text from ICH-E2E with additional commentary on implementation within the EU. On the basis of the safety profile, MAA/MAH should consider carefully whether there would be a need for risk minimisation measures to be introduced. If no such measures are thought necessary the MAA/MAH should provide a full justification within Part II of the EU-RMP. Similarly, every time the Plan is updated (see section 4.13) the company should reconsider its position vis-à-vis the need for risk minimisation and Part II should be updated accordingly.

4.3 Situations when an EU-RMP is required

An EU-RMP may need to be submitted at any time of a product's life-cycle – ie during both the pre-authorisation and post-authorisation phases. In particular an EU-RMP should be submitted:

- with the application for a new marketing authorisation for :
  - any product containing a new active substance
  - a biosimilar product
  - a generic product where a safety concern has been identified with the innovator product
- with an application involving a significant change in a marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant new indication) unless it has been agreed with the Competent Authority that submission is not required.
- on request from a Competent Authority (both pre-and post- authorisation).

On the initiative of an MAA/MAH when they identify a safety concern with a product at any stage of its life cycle.

4.4 Location in the dossier

An EU-RMP submitted at the time of an application for a Marketing Authorisation should be provided in Module 1.x (to be confirmed) of the Marketing Authorisation Application in a stand-alone format allowing circulation to, and evaluation by pharmacovigilance and risk management experts. It should be accompanied by other relevant documents such as study protocols, where applicable.

Updates to the EU-RMP should be presented preferably in a tab-separated dossier and in accordance with the appropriate headings and numberings of the EU-CTD format. This should be accompanied by a cover letter, detailing which sections of the EU-RMP have been changed, and study reports (if appropriate.)

4.5 Safety Specification

The Safety Specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-authorisation period. The Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan.

In the EU-RMP the Safety Specification will also form the basis of the Risk Minimisation Plan.

It is recommended that MAH/MAAs follow the structure of elements provided below when compiling the Safety Specification. The elements of the Safety Specification that are included are only a guide.

The Safety Specification can include additional elements, depending on the nature of the product and its development program. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

4.5.1 Non-clinical

Within the Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.)
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.)
- Drug interactions
- Other toxicity-related information or data.

The relevance of the findings to the use in humans should be discussed. If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

4.5.2 Clinical

4.5.2.1 Limitations of the human safety database

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

In order to assess the limitation of the human safety database, the size of the study population should be detailed using both numbers of patients and patient time (patient-years, patient–months) exposed to the drug. This should be stratified, for relevant population categories such as age and gender, type of study (e.g. randomised controlled trial, open clinical trial, observational study) and any other relevant variable, such as dose, indication and duration of treatment. Limitations of the database should also be presented in terms of the frequencies of adverse drug reactions detectable given the size of the database. The limitations of the database should also be discussed with regard to suspected long-term adverse drug reactions (e.g. malignancies) when it is unlikely that exposure data is of sufficient duration and latency.

Post-marketing (non study) exposure

Where marketing of the medicine has occurred, the MAH should provide data on patients exposed post marketing. Exposure data based on the number of kilograms of drug sold divided by the average dose is only valid if the drug is always taken at one dose level for a fixed length of time. In paediatric populations or mixed populations of different indications or age groups use of this measure alone is inappropriate.

A more accurate breakdown of drug exposure based on market research should be provided where possible. When deciding which measure to use for exposure data, it is important to consider the way a medicine is used. For example, for medicines used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation is determined by pack size – e.g. a course of antibiotics -, a simple count of packs sold may be more appropriate. The information should be stratified by relevant variables such as age, indication, dose and duration of treatment.

4.5.2.2 Populations not studied in the pre-authorisation phase

The Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-authorisation phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed.

Limitations of the database should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population, in particular when exclusion criteria are not proposed as contraindications for the drug. In discussing differences between target populations and those exposed in clinical trials it should be noted that some differences might arise through trial setting – e.g. hospital or general practice – rather than through explicit inclusion/exclusion criteria.

Populations to be considered for discussion should include (but might not be limited to):

- Children
- The elderly
- Pregnant or lactating women
- Patients with relevant co-morbidity such as hepatic or renal disorders
- Patients with disease severity different from that studied in clinical trials
- Sub-populations carrying known and relevant genetic polymorphism
- Patients of different racial and/or ethnic origins

Post Marketing Experience

For updates to the Safety Specification, specific reference should be made to how the realised pattern of exposure has differed from that predicted, including off-label use.

Newly identified safety issues should be mentioned, in particular any issue found in relation to a population not studied in the pre-approval phase should be discussed along with the implications for the Summary of Product Characteristics.

If regulatory action has been taken in relation to a safety issue, this should be mentioned.

4.5.2.3 Adverse Events/Adverse Reactions

This section should list the important and potential risks that require further characterisation or evaluation.

Identified risks that require further evaluation

More detailed information should be included on the most important identified adverse events/adverse drug reactions, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These adverse events/adverse reactions should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g. frequency in normal conditions of use, severity, outcome, at-risk groups, etc.).

Potential risks that require further evaluation

Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterise the association.

Potential for overdose

Special attention should be given in particular cases e.g. where there is a narrow therapeutic margin, a product with significant toxicity and or potential for overdose, a known or anticipated risk of significant interactions with other products or food, or parenteral routes of administration.

Presentation of risk data

The frequency of important adverse events/adverse reactions should be expressed taking into account the source of the data. For a product already on the market, the reporting rate based on the number of spontaneously reported adverse events/ adverse reactions (in the numerator) and the sales data (in the denominator) should not be presented as an estimate of the rate of occurrence of an adverse reaction in an exposed population. Adverse event/ adverse reaction frequencies should always be based on systematic studies (e.g. clinical trials or epidemiological studies) in which both the number of patients exposed to the drug and the number of patients who experienced the respective adverse event/ adverse reaction are known.

The denominator should be expressed using the appropriate measure: eg number of patients or in patient-time or equivalent units (courses of treatment, prescriptions...). However, when using patient-time, the assumed hazard function must be nearly constant over time. Otherwise it should be split into relevant categories where the assumption of constancy holds. The incidence rate of an adverse event/adverse reaction can be expressed as an incidence proportion (patient units in the denominator) or an incidence density (patient-time units in the denominator), with its 95% confidence interval. Where appropriate, the period of major risk should be identified. Adverse event/adverse reaction incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess and relative incidence should be given. Excess incidence (in comparison to placebo and active comparator; if available) should be calculated based on the best available evidence (e.g. meta-analytic techniques) for each population (total controlled, total controlled plus open label extension, total study). Time to event data should be summarised using survival techniques which take appropriate account of informative censoring. Cumulative hazard functions may provide a simple visual comparison of the competing risks of different adverse events. These data can be stratified by substance (to investigate the difference in the adverse event profile between active and placebo), or by risk factors such as dose, gender or age.

The potential impact of the most important identified and potential risks should be addressed using for example: strength of evidence, supporting plausibility, nature of evidence and potential public health burden, morbidity and case fatality. Recording this in a structured form will facilitate assessment of the potential significance of a safety concern. Classification of the safety concern by dose, time and susceptibility status (patient-related risk factors) is encouraged.[1] The identification of susceptible patients should receive specific attention, possibly from analysis of cases. It is likely that these adverse events/ adverse reactions will require further evaluation as part of the Pharmacovigilance Plan.

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[1] Aronson JK and Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ 2003; 327:1222-5.

4.5.2.4 Potential for medication errors

MAAs/MAHs are encouraged routinely to consider the likelihood of medication errors. In particular, they should assess prior to marketing, common sources of medication errors. During the development phase and during the design of the product for marketing, the applicant needs to take into account potential reasons for medication error. The naming (taking into account the Guideline on the acceptability of Invented Names for human medicinal products processed through the centralised procedure), presentation (e.g. size, shape and colouring of the pharmaceutical form and packaging), instructions for use (e.g. regarding reconstitution, parenteral routes of administration, dose calculation) and labelling are among the items to be considered.

If a product has life-threatening potential when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is common practice to administer the product at the same time as other medicinal products given by the hazardous route.

The need for visual (or physical) differentiation between strengths of the same product and between other products commonly administered or taken at the same time should be discussed. When a product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error.

Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

Medication errors identified during product development should be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been taken into account in the final product design.

4.5.2.5 Potential for illegal use

The potential for illegal use should be considered. If appropriate, means of limiting this, e.g. by the use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed.

4.5.2.6 Potential for transmission of infectious agents

The MAA/MAH should discuss the potential for the transmission of an infectious agent in line with the "Guideline on reporting requirements regarding the transmission of infectious agents via medicinal products" *(title to be confirmed)*

4.5.2.7 Identified and potential interactions including food-drug and drug-drug interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed.

It should be stated which interactions require further investigation.

4.5.2.8 Epidemiology

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed (because the epidemiology of the indication(s) may vary across regions), but the emphasis should be on the epidemiology in the EU.

In addition, for important adverse events that may require further investigation, it is useful to review the incidence rate of these events among patients in whom the drug is indicated (ie the background incidence rates). Information on risk factors for an adverse event would also be useful to include, if available. For example: if a drug is intended for treating prostate cancer the target population are likely to be men over the age of 50 years. This population is also at increased risk of myocardial infarction. If it is suspected that the drug might also cause myocardial infarction, it would be useful to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not on the drug

4.5.2.9 Pharmacological class effects

The Safety Specification should identify risks believed to be common to the pharmacological class.

If a risk which is common to the pharmacological class is not thought to be a safety concern with the drug, this should be justified.

4.5.3 Summary

At the end of the Safety Specification a summary should be provided of the:

- Important identified risks
- Important potential risks
- Important missing information.

Based on this summary the MAA/MAH will provide a Pharmacovigilance Plan and an evaluation of the need for a Risk Minimisation Plan (see template in annex X.)

4.6 <u>Pharmacovigilance Plan</u>

According to ICH E2E, the Pharmacovigilance Plan should be based on the Safety Specification and propose actions to address the safety concerns identified. Early discussions between Competent Authorities and the Applicant or Marketing Authorisation Holder are recommended to identify whether, and which, additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and the Pharmacovigilance Plan will not replace but rather complement the procedures currently used to detect safety signals.

4.6.1 Routine Pharmacovigilance Practices

For medicines where no safety concerns have arisen, routine pharmacovigilance should be sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies).

A description of routine pharmacovigilance activities is covered in Volume 9 of the Rules governing medicinal products in the EU and "The guideline on monitoring of compliance with Pharmacovigilance regulatory obligations and Pharmacovigilance inspections for Centrally Authorised Products" and should be consulted in developing the Pharmacovigilance Plan.

4.6.2 Additional pharmacovigilance activities and action plans

For products with important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered.

Marketing authorisation holders should identify when these conditions apply. An example of this might be when a potential risk with an individual medicinal product has a significant background incidence in the target population(s) leading to difficulties in distinguishing between the effects of the

drug and the "normal" incidence. When any doubt exists about the need for additional pharmacovigilance activities, consultation with a Competent Authority should be considered.

The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For important missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

The threshold for investigating a safety concern further will depend upon the indication, the target population and the likely impact on public health. For example, a safety concern with a vaccine might have a lower threshold for investigation than the same issue in a medicine used in the palliative treatment of metastatic cancer.

Annex A lists some of the epidemiological tools which might be considered for inclusion in a Pharmacovigilance Plan. Additional pharmacovigilance activities included in the Pharmacovigilance Plan should be designed and conducted according to the recommendations in the Guidelines for Good Pharmacoepidemiology Practices (GPP)[1]. For studies involving children, the "Guideline on conduct of pharmacovigilance for medicines used by the paediatric population" should be consulted. The responsibility for the scientific value of study protocols remains with Applicants or Marketing Authorisation Holders, even if they have been previously discussed with Competent Authorities.

4.6.3 Action Plan for safety concerns

The plan for each important safety concern should be presented and justified according to the following structure (see also annex X):

- Safety concern
- Objective of proposed action(s)
- Action(s) proposed
- Rationale for proposed action(s)
- Monitoring by the MAA/MAH for safety concern and proposed action(s)
- Milestones for evaluation and reporting.

Protocols (draft or otherwise) should be provided. Details of the monitoring for the safety concern for a clinical trial could include: stopping rules, information on the drug safety monitoring board and when interim analyses will be carried out.

Although not explicitly included in this structure, it is also necessary in the EU-RMP to explain the decision-making processes which will depend on the outcomes of the proposed actions. The possible consequences of the study outcomes should be discussed.

4.7 Evaluation of the need for a Risk Minimisation Plan

On the basis of the Safety Specification and Pharmacovigilance Plan, the Marketing Authorisation Applicant (MAA) / Marketing Authorisation Holder (MAH) should provide an evaluation of the need

[1] Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, http://www.pharmacoepi.org/resources/guidelines_08027.cfm, August 2004

for specific risk minimisation measures. If these are required they should be described in the Risk Minimisation Plan and included within the EU-RMP.

For each safety concern, the MAA/MAH should assess whether any risk minimisation actions are needed. Some safety concerns may be adequately addressed by the proposed actions in the Pharmacovigilance Plan, but for others the risk may be of a particular nature and seriousness that risk minimisation actions are needed. It is possible that the risk minimisation activities may be limited to ensuring that suitable warnings are included in the product literature or by the careful use of labelling and packaging. If a MAA/MAH is of the opinion that no additional action beyond this is warranted, this should be discussed and, where appropriate, supporting evidence provided. As a rule MAAs/MAHs should always consider the need for risk minimisation measures whenever the safety specification is updated in the light of new safety information on the medicinal product.

The evaluation should consider each of the issues identified in the Safety Specification, including a brief assessment of the potential for specific measures to reduce medication errors, illegal use or the transmission of infectious agents.

4.8 The Risk Minimisation Plan

The Risk Minimisation Plan details the actions which will be taken to reduce the risks associated with an individual safety concern. An individual safety concern may have more than one risk minimisation action attached to an objective. For example, a possible plan for a known teratogen could have the objective of avoiding any patient taking the drug becoming pregnant. One action might be to develop an educational pack to provide information to the patients on the risks of the medicine and the need for contraception. Another might be to put the need for effective contraception in the Summary of Product Characteristics and a recommendation that patients should have a negative pregnancy test before each prescription. It might also be an action to limit the pack sizes to one month's supply of the medicine.

The Risk Minimisation Plan should list the safety concerns for which specific risk minimisation actions are proposed. For each safety concern the following headings in the plan will mirror those for safety concerns listed in 4.6.2. Additionally, however, a section will be included detailing how the effectiveness of the measures to reduce risk will be assessed (see annex X).

4.9 Risk minimisation tools

It is difficult to provide precise guidance on which tool should be used in a given situation as each issue needs to be considered on a case-by-case basis. Some of the tools are described in Annex B but it is essential that appropriate specialised experts should be consulted at all stages and marketing authorisation applicants and holders are also encouraged to discuss plans with the competent authorities (Member States or EMEA as appropriate) early on.

4.9.1 Risk communication

Accurate and timely communication of emerging data on risk is an essential part of pharmacovigilance. Risk communication is an important step in risk management as well as a risk minimisation tool. Patients and health care professionals need accurate and well-communicated information about the risks associated with both the medicine, and the condition for which it is being used, so that an informed choice can be made about the most appropriate treatment. The product literature in the form of the Summary of Product Characteristics and Patient Information Leaflets is an important means of informing prescribers and patients about the risks associated with a particular medicine but additional materials may be needed. A short list of established media for such communication is given in Annex B (under additional educational material) but the target audience, levels of detail required to achieve effective results and the most appropriate forms of words will all vary with circumstances. Because of the importance of risk communication it is recommended that appropriate experts be consulted. Further guidance is being developed on this topic.

4.10 The Marketing Authorisation

Restrictions and conditions within the marketing authorisation may be used as a risk minimisation measure (see Annex B). When a marketing authorisation is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which the medicinal product may be made available to patients. These conditions may also be modified when the MA is amended in the post-authorisation phase. This is commonly referred to as the "legal status" of a medicinal product. It may also restrict where the medicine can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist). For medicines only available upon prescription, additional conditions may be imposed by classifying medicines into those available only upon either a restricted medical prescription or a special medical prescription.

The CHMP or National Competent Authorities may also make recommendations on conditions or restrictions with regard to the safe and effective use of the medicinal product. In the case of the CHMP, these conditions or restrictions will usually only affect the Decision addressed to the Marketing Authorisation Applicant. However, in certain circumstances, the Commission may also decide to adopt a Decision addressed to the Member States.

4.11 Ensuring the effectiveness of risk minimisation tools

The definition of risk management requires assessment of the effectiveness of activities and interventions forming part of the process. It is clearly desirable that measures which may involve substantial investment of effort and resources should be shown to achieve the desired effects. In addition, as a public health measure it is imperative that alternative methods be adopted should a particular risk minimisation strategy prove ineffective. Assessment of effectiveness will also increase understanding of which tools are most appropriate in addressing specific types of safety concerns.

4.11.1 Assessment of risk minimisation

Direct measurement of risk reduction should be employed whenever feasible. Surrogate measures should be considered when this is not feasible or to provide interim assessments whilst awaiting direct risk reduction measurements. For example, for measures based on the provision of information to professionals, descriptive studies or surveys which assess whether the information is being effectively communicated might be appropriate. The use of medical databases might also allow direct measures of how uniformly such advice was being adhered to by reviewing, for example, concomitant medication or the results of laboratory tests. Since such studies are likely to be required with increasing frequency, the availability of such databases will be an ever more important factor in risk management. If the prescribing databases are further linked to patient clinical outcome, a study of the adequacy of the prescribing process could be designed to evolve over time into a full risk reduction study.

It is clear that, even when risks are of a type which can be directly measured, ethical and practical considerations may prevent prospective comparison. It may be scientifically difficult to make direct comparison between a situation with and without the intervention to be assessed and may not be achievable in timescales which allow the lessons learned to be used to improve the risk management process. In particular this will occur when risks associated with long-term exposure or very rare events are to be reduced. For products which a risk minimisation plan has been introduced after some time on the market a comparison with historical data can be made. Not withstanding the above, MAAs/MAHs should investigate new methodologies for monitoring and assessment.

4.12 Summary of actions in the EU-Risk Management Plan

The EU-RMP should contain an overall summary of the actions detailed for the product. This should be in two parts:

- Summary of actions for each safety concern
- Summary of all actions and their milestones.

The relationship between actions and safety concerns may be clarified by a cross-tabulation of the two categories showing which concerns are addressed by each action (see annex X.)

Summary of actions for each safety concern

This should be a simple table listing each safety concern and summarising the actions which will be taken. It should provide a cross reference to the actions in the Pharmacovigilance Plan and the Risk Minimisation Plan for the individual safety concern.

Summary of actions and milestones

This section of the EU-RMP for the product should be organised in terms of the actions to be undertaken and their milestones. The reason for this is that one proposed action (e.g., a prospective safety cohort study) could address more than one of the identified safety concerns. Timelines and milestones should be included in the summary with a timetable for the submission of findings. In developing these milestones one should consider:

- When it will be possible to detect an adverse reaction with a pre-defined frequency at a pre-defined confidence level. This frequency should be chosen such as to reflect an acceptable level of risk for patients and public health, or

- When it will be possible to assess with sufficient precision the effect of risk factors associated with the occurrence of an adverse reaction.

- When the results of ongoing or proposed safety studies are expected to be available

- The seriousness and magnitude of the risk for which risk minimisation actions are being proposed. Evaluation of the effectiveness of the actions will need to be carried out earlier and more frequently if the risk is very serious.

4.13 Submission of updated EU-RMP documents.

As additional information on the safety of a medicinal product becomes available, the Safety Specification and other sections of the EU-RMP should be updated accordingly. For example, spontaneous reports, clinical trials and pharmacoepidemiological studies may all give rise to safety signals which need to be investigated or the results from a study could provide missing information to update the Safety Specification. It may be that, based on the new information, it can be concluded that the safety concern has been resolved and that no further actions are needed beyond routine pharmacovigilance. In other cases, additional activities may be proposed and new milestones should be developed.

The updated EU-RMP should be submitted at the same time as the next periodic safety update report (PSUR) unless other requirements have been laid down as a condition of the marketing authorisation. In addition, an updated EU-RMP should be submitted:

- when new information is received that may impact on the current Safety Specification or Pharmacovigilance Plan.

- within 60 days of an important (Pharmacovigilance or Risk Minimisation) milestone being reached or the results of a study becoming available.

at the request of the Competent authority.

PSURs

A summary of any amendments made to the EU-RMP should be included in the PSUR (Section 2.8.3 Addendum to ICH E2C clinical safety data management. Periodic safety update reports for marketed drugs CPMP/ICH/4679/02).

5. PROPOSED TIMETABLE[1]

<Text>

6. DEFINITIONS

Safety concern

An important identified risk, important potential risk or important missing information

Identified risk

Adverse event for which there is adequate evidence of an association with the medicinal product of interest. Examples are:

- an adverse drug reaction adequately demonstrated in non-clinical studies but not resolved by clinical data
- an adverse drug reaction observed in well-designed clinical trials or epidemiological studies and for which a statistically significant difference has been found with the comparator group (placebo or active substance, or unexposed group) on a parameter of interest such as the rate ratio or the rate difference
- an adverse drug reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

Potential risk

Adverse event for which there is some basis for suspicion of an association with the medicinal product of interest but for which this association has not been confirmed. Examples are:

- non-clinical safety findings that have not been observed or adequately addressed in clinical studies
- adverse events observed in clinical trials or epidemiological studies for which a difference from the comparator group (placebo or active substance, or unexposed group) on the parameter of interest is not statistically significant
- a signal arising from a spontaneous adverse reaction reporting system
- an event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.

[1] Including timetable for discussion with other concerned working parties. See also cover page. (For draft guidelines only).

Important identified risk, important potential risk or important missing information

An identified risk, potential risk or missing information that could impact on the risk- benefit balance of the product or have implications for public health.

Missing information

Information about the safety of a medicinal product which is not available at the time of submission of the EU Risk Management Plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

Population potentially at risk

A population which has not been studied, or has only be studied to a limited degree, in clinical investigations of the product, but which is likely to be exposed to the product based on the Summary of Product Characteristics (e.g. elderly or pregnant women).

Routine pharmacovigilance

Pharmacovigilance activities specified in Regulation 726/2004 and Directive 2001/83/EC as amended that should be conducted for all medicinal products.

Risk management system

A Risk management system is a set of pharmacovigilance activities and interventions designed to proactively identify, characterise and prevent or minimise risks relating to medicinal products, including risk communication and the assessment of the effectiveness of risk minimisation interventions.

Risk minimisation

This is a set of activities used to reduce the probability of an adverse drug reaction occurring or its severity should it occur.

ANNEX A: EPIDEMIOLOGICAL METHODS FOR POST-AUTHORISATION SAFETY STUDIES

1. STUDY DESIGNS

Post-authorisation safety studies may adopt different designs depending on their objectives. A brief description of the fundamental types of studies, as well as the types of data resources available, is provided thereafter. However, the present document does not have the intention to be exhaustive and must be complemented with other widely available sources[1-4]. The ICH-E2E guideline has been followed to a great extent in order to provide a harmonized view on this topic.

Spontaneous reporting schemes are valuable tools for providing safety signals in a continuous manner. In many occasions, however, such passive surveillance should be complemented with more formal approaches in order to increase the sensitivity for risk identification or confirm, characterise or quantify possible hazards. These more formal approaches are included under the generic denomination of post-authorisation safety studies and may adopt a variety of designs.

1.1 Methods for active surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

1.1.1 Sentinel sites

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as the potential for abuse, can be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, haemodialysis centres, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

1.1.2 Intensive Monitoring Schemes

Intensive monitoring is a system of record collation in designated areas e.g. hospital units or by specific physicians in community practice. The competent authority may be involved in the drawing up of the protocol to undertake this collection of data or will be informed that such monitoring is taking place. Furthermore, it may be considered appropriate in the authorisation of certain medicinal products to impose specific requirements in respect of reporting serious or unexpected reactions on the prescribing physician and to make these requirements a condition of use of the product under the terms of the marketing authorisation. The relevant pharmacovigilance centre should ensure that data and reports are collected at agreed intervals and in an appropriate format.

1.1.3 Drug event monitoring

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire[5,6] Limitations of drug event monitoring include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

1.1.4 Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (exposure or drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition, or from outside the registry.

Exposure (drug) registries address populations exposed to medicinal products of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

1.2. Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).

1.2.1. Cross-sectional study (survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

1.2.2. Cohort study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of

interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes. Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

1.2.3. Case-control study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease among the exposed as compared to the non-exposed. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events (or actually, effect-modifiers). Risk factors can include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

When the source population within which the case-control study is conducted is a well-defined cohort, it is then possible to select a random sample from it to form the control series. The name "nested case-control study" has been coined to designate those studies in which the control sampling is density-based (e.g. the control series represents the person-time distribution of exposure in the source population). The case-cohort is also a variant in which the control sampling is performed on the persons integrating the source population regardless the time they may have contributed.

A case-control approach could also be set up as a permanent scheme to identify and quantify risks (case-control surveillance). This strategy has been followed for rare diseases with a relevant etiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders.

1.2.4. Other novel designs

Some novel designs using only a sample of the cases have been described to assess the association between intermittent exposures and short-term events, including the case-series, the case-crossover and the case-time-control studies. In these designs the control information is obtained from past person-time experience of the cases themselves. One of the important strengths of these designs is that those confounding variables that do not change within individuals are automatically matched.

1.3. Clinical Trials

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions.

Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted.

In performing clinical trials the Good Clinical Practice guideline should be followed.

1.4. Other studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

1.4.1. Occurrence of disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective1. For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses

1.4.2. Drug utilization study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies may include a lack of clinical outcome data or information of the indication for use of a product.

2. DATA SOURCES

Pharmacoepidemiologic studies can be performed using a variety of data sources. Traditionally, field studies were require to retrieve the necessary data on exposure, outcomes, potential confounders and

other variables, through interview to appropriate subjects (e.g. patients, relatives etc.) or by consulting the paper-based medical records. However, the advent of automated healthcare databases has remarkably increased the efficiency of pharmacoepidemiologic research. There are two main types of automated databases, those which contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes which require a record-linkage between pharmacy claims and medical claims databases. These datasets may include millions of patients and allow for large studies. They may not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data, and paper-based medical records should be consulted to ascertain and validate test results and medical diagnoses. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. There are many databases in place for potential use on pharmacoepidemiological studies, or in their validation phase for future use.

Establishing national and international networks of researchers are increasingly viewed as an alternative approach for some pharmacoepidemiological studies when there is no database available, or those existing are either underpowered or they do not gather the relevant information. Establishment of long-term registries and/or case-control surveillance from such networks may be particularly benefited.

With any data source used the privacy and confidentiality regulations that apply to personal data should be followed. The anonymisation of medical records when feasible is the best option.

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ANNEX B: METHODS FOR RISK MINIMISATION

1. RISK MINIMISATION

The tools for risk minimisation can be divided into those where a reduction in risk is achieved primarily through the provision of information and education and those which seek to control the use of the medicine. When it is obvious that a risk minimisation tool will be needed post authorisation, consideration should be given to piloting the tool during the development phase to see the effectiveness and suitability. When this is done, the outcome should be provided in the risk minimisation plan under the appropriate action.

1.1 Provision of information

Provision of information to healthcare professionals and/or patients on the specific risks of a product and the measures on how to reduce them is an essential tool of risk management. This provision of information may be confined to information contained within the Summary of Product Characteristics and Package Leaflet or may be through the use of educational material. The need for additional material beyond the Summary of Product Characteristics and Package Leaflet will depend upon the risk and should be considered on a case-by-case basis. Experts in risk communication should be consulted as appropriate.

1.1.1 Additional Educational Material

The need for additional educational material and the form in which it should be provided will depend upon the specific safety concern. The aim of a specialised educational programme for healthcare professionals and/or patients is to:

- Enhance understanding of the specific risk(s) and methods to reduce either the frequency or severity
- Enhance patient information, awareness and provide information on the need and use of additional precautions.

The educational programme may include but is not limited to the following materials:

- Healthcare professional letters
- Physician's Guide to prescribing
- Pharmacist's Guide to dispensing
- Checklists for assessing comprehension, knowledge, attitudes, and/or desired safety behaviours about the risk(s). These should be tailored to the target audience (e.g. physicians, pharmacists or patients)
- Checklists for actions before prescribing or dispensing
- Patient information Brochures
- Specific training programmes

The choice of media may also need to be considered (written, audio or video) as well as the use of drawing/symbols to improve understanding. For medicines where the target population may include a larger proportion of visually impaired patients, the use of Braille or audio media should be given special consideration. Pre-testing materials in the target audience(s) is highly desirable to help ensure

good comprehension and acceptance of the communication method and contents. A variety of testing methods such as readability testing, focus groups or surveys could be used.

Specific training programmes may be considered in certain circumstances. However, it is unlikely that prescription/dispensing of the medicine can be limited to people who have undertaken such a programme.

The above educational materials should be in strict compliance with the contents of the SPC and the Patient Information Leaflet and must be agreed with the Competent Authority.

1.2 Legal Status of a Medicine

It is possible that controlling the conditions under which a medicine may be made available could reduce the risks associated with its use or misuse. This might be achieved by control of either who may be permitted to prescribe or dispense a medicine or by controlling who, or the conditions under which a patient, may receive a medicine.

When a marketing authorisation is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which the medicinal product may be made available to patients. This is commonly referred to as the "legal status" of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medical prescription. It may also restrict where the medicine can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist).

For medicines only available upon prescription, additional conditions may be imposed by classifying medicines into those available only upon either a restricted medical prescription or a special medical prescription. When considering classification as subject to restricted medical prescription the following factors shall be taken into account:

- the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment,

- the medicinal product is used for the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow up may be carried out elsewhere, or

- the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment.

In the case of an application for a marketing authorisation submitted in accordance with the Centralised procedure, the CHMP is responsible for recommending the Legal Status to the Commission. Although the use of legal status is not a tool that can be used directly by a MAA for the purposes of risk reduction, the MAA could request the Competent authority to consider a particular legal status.

However, the definition of what constitutes a specialist is not uniform throughout the Member States so in practice the provisions of the last indent are usually phrased in the section 4.2 of the Summary of Product Characteristics as: "treatment by a physician experienced in the treatment of <the disease>". Although restriction to use in a hospital environment may in practice ensure that the medicine is always prescribed by a specialist, this needs to be balanced against the inconvenience to patients if they need to attend a hospital for every prescription. Care also needs to be taken when considering where a medicine can be safely administered. For example the term "clinic" has different connotations depending upon the country. For this reason, the type of equipment needed may be specified rather than a location: e.g.; "use in a setting where resuscitation equipment is available."

For classification as subject to special medical prescription the following factors shall be taken into account:

- the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within he meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971, or

- the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or

- the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the previous indent as a precautionary measure.

There is possibility of implementing further sub-categories at Member State Level which permits the Member States to tailor the broad classifications described above to their national situation. The definitions and therefore also the implementation varies in those Member States where the sub-categories exist.

1.3 Control at pharmacy level

The control of dispensing is another potential tool for risk management. Pharmacists who are well informed about the risks of a medicine can help educate the patient and provide an additional level of protection.

1.4 Control of prescription size or validity

Limiting the validity of a prescription is another tool for risk management in the situation where decision to prescribe depends upon the result of a test which is only valid for a specific time. In some Member Sates it is possible to limit the validity of a prescription but not in others.

Limiting the number of units prescribed is another risk management tool. This can be useful if regular testing or review is needed. By limiting the number of units, the patient will need to see a healthcare professional at defined intervals increasing the opportunity for testing and reducing the length of time a patient is without review. If this strategy is adopted, it is a pre-requisite that the appropriate pack size is available and that supply issues are addressed. In extreme cases, making units available in only one pack size to try to link prescribing to the need for review may be considered.

A small pack size can also be useful, especially if overdose is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled.

1.5 Informed consent and other patient aspects

In a clinical trial, patients are given information about the possible benefits and risks of the trial medication and any procedures associated with the trial. The patient signs a form to say that they have been given the information, they understand it and agree to take part in the trial. This is known as informed consent. It has potential as a risk management tool to ensure that patients have been provided with appropriate information regarding the risks of the medicine and appropriate measures to reduce the risks. Use of informed consent outside the clinical trial area may not be possible in some Member States.

1.6 Restricted access programmes

In high-risk situations, it may be necessary to restrict access to a medicinal product to those patients who agree to take part in a specific surveillance programme.

1.7 Patient registries

Patient registries are often suggested as a means of risk management. They have been used (sometimes very successfully) in individual countries to record the results of tests, to ensure that the recommended conditions of use are being adhered to, and control access to a medicine. However, there are possible issues about who controls the registry and the confidentiality of medical data.

Whereas patient registries could be a very useful tool for pharmacovigilance studies to characterise risks, use as a means of controlling access is not currently possible in some Member States. It is strongly suggested that if a MAH is contemplating the use of a patient registry, this should be discussed with the appropriate regulatory authority at a very early stage.

ANNEX C: EU-RMP TEMPLATE