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3 Guideline on good pharmacovigilance practices (GVP)

4 Module XVI– Risk minimisation measures: selection of tools and effectiveness 5 indicators

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Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu.

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XVI.A. Introduction

Risk minimisation measures are public health interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. Planning and implementing risk minimisation measures and assessing their effectiveness are key elements of risk management.

The guidance provided in this Module should be considered in the context of the wider GVP guidance, in particular in conjunction with Module V.

Risk minimisation measures may consist of routine risk minimisation or additional risk minimisation measures. Routine risk minimisation is applicable to all medicinal products, and involves the use of the following tools, which are described in detail in Module V:

- the summary of product characteristics (SmPC)
- the package leaflet
- the labelling
- the pack size and design
- the legal (prescription) status of the product

The majority of safety concerns may be adequately addressed by routine risk minimisation measures (see Module V). For some risks however, routine risk minimisation measures will not be sufficient and additional risk minimisation measures will be necessary to manage risk and/or improve the risk-benefit balance of a medicinal product. This Module provides particular guidance on the use of additional risk minimisation measures and on the selection of tools. However, it should be understood that the principles for evaluating the effectiveness of risk minimisation measures may also be applicable to the evaluation of routine risk minimisation measures particularly where important for the risk-benefit balance of the product.

On the basis of the safety concerns described in the safety specification (see Module V), the appropriate risk minimisation measures should be determined. Each safety concern needs to be individually considered and the selection of the most suitable risk minimisation measure should take into account the seriousness of the potential adverse reaction(s) and its severity (impact on patient), its preventability or the clinical actions required to mitigate the risk, the indication, the route of administration, the target population and the healthcare setting for the use of the product. A safety concern may be addressed using more than one risk minimisation measure, and a risk minimisation measure may address more than one safety concern.

Directive 2001/83/EC indicates that the marketing authorisation holder shall “monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a” (DIR Art 104 (2) (d)). The Directive and Regulation (EC) No 726/2004 also include provisions for the Agency and the national competent authorities to monitor the outcome of risk minimisation measures which are contained in the risk management plans (RMPs) or measures that are laid down as conditions.

This Module provides guidance on the principles for:

- the development and implementation of additional risk minimisation measures, including examples of risk minimisation tools;
- the evaluation of the effectiveness of risk minimisation measures.

XVI.B describes the development, implementation and co-ordination of risk minimisation measures and the general principles of the evaluation of their effectiveness. XVI.C considers the application of those meassures and principles in the setting of the European regulatory network.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

XVI.B. Structures and processes

XVI.B.1. General principles

Risk minimisation measures aim to optimise the safe and effective use of a medicinal product throughout its life cycle. The benefit–risk balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimising benefit, through targeted patient selection and/or exclusion and through treatment management (e.g. specific dosing regimen, relevant testing, patient follow-up, etc). Risk minimisation measures should therefore guide optimal use of a medicinal product in medical practice with the goal of supporting the provision of the right drug, at the right dose, at the right time, to the right patient, by the right prescriber, and with the right information and monitoring.

The majority of safety concerns are addressed by routine risk minimisation measures (see Module V). For some risks however, routine risk minimisation will not be sufficient and additional risk minimisation measures will be necessary.

A variety of tools are currently available for additional risk minimisation. This field is in a continuous stage of development, and new tools are likely to be developed in the future. Technology advances, such as interactive web-based tools may gain prominence in the future in addition to the paper-based information and educational materials.

Successful implementation of additional risk minimisation measures requires contributions from all impacted stakeholders, including marketing authorisation applicants or holders, patients and healthcare professionals. The performance of these measures in healthcare systems requires assessment to ensure that their objectives are fulfilled and that the measures in place are proportionate taking account of the risk-benefit profile of the product and the efforts required of healthcare professionals and patients to implement the measures. It is therefore important to ensure that additional risk minimisation measures have a clearly defined objective relevant to the minimisation of specific risks and/or optimisation of the risk-benefit profile. Clear objectives and defined measures of success with milestones need to guide the development of additional risk minimisation measures and close monitoring of both their implementation and ultimate effectiveness is necessary. The nature of the safety concern in the context of the risk-benefit profile of the product, the therapeutic need for the product, the target population and the required clinical actions for risk minimisation are factors to be considered when selecting risk minimisation tools and an implementation strategy to accomplish the desired public health outcome. The evaluation of effectiveness should facilitate early corrective actions if needed.

The risk minimisation plan, an integral part of the RMP (see Module V), should therefore give appropriate consideration to the following points:

- Rationale for additional risk minimisation measure (linked to specific safety concerns): This section should set out the rationale for the proposed additional risk minimisation measure(s) which should include defined objective(s) for each of the measures proposed. There should be a clear description of how the additional risk minimisation measure proposed will address a specific safety concern;

- Description of additional risk minimisation measure(s): This section should provide a description of the selected additional risk minimisation measures, including a description of the tools that will be used and key elements of content;
- Implementation plan: This section should provide a detailed proposal for the implementation of additional risk minimisation measures (e.g. setting and timing or frequency of intervention, details of the target audience);
- Evaluation plan: This section should provide a detailed plan with milestones for evaluating the effectiveness of additional risk minimisation measures in process terms and in terms of overall health outcome measures (e.g. reduction of risk).

XVI.B.2.Risk minimisation measures

Risk minimisation measures aim to facilitate informed decision making to support risk minimisation when prescribing, supplying and/or using a medicinal product. While routine measures are applied to every medicinal product (see details in Module V) additional risk minimisation activities should only be proposed when they are laid down as conditions for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people.

Additional risk minimisation measures may differ widely in purpose, design, target audience and complexity. These measures might be used to guide appropriate patient selection with the exclusion of patients where use is contraindicated, to support on-treatment monitoring relevant to important risks and/or management of an adverse reaction once detected. Additionally, specific measures may be developed to minimise the risk of medication error and/or to ensure appropriate administration of the product where it is not feasible to achieve this through the product information and labelling alone.

If additional risk minimisation activities are requested, the rationale for the request should be clearly documented, should be linked to specific safety concerns and sufficiently detailed in implementation and evaluation planning.

XVI.B.2 describes risk minimisation measures that should be considered in addition to the routine measures, including:

- educational programme;
- controlled access programme;
- other risk minimisation measures.

XVI.B.2.1. Educational programme

Many additional risk minimisation tools that can be used in an educational programme are based on targeted communication with the aim to supplement the information in the summary product characteristics (SmPC) and package leaflet. Any educational material should be clearly focused on defined risk minimisation goals, providing clear and concise messages.

The aim of an educational programme is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimising risk. Educational materials should therefore be built on the premise that there is an actionable recommendation for targeted education and that applying this measure is considered important for minimising an important risk and/or for optimisation of the risk-benefit profile. In the context of an educational programme, the tools can have several different target audiences, can address more than one concern and can be delivered using a combination of tools and media (paper, audio, video, web, in-person training). Ideally, materials

should be available in a range of formats so as to ensure that access is not limited by disability or access to the internet.

The content of any educational material should be fully aligned with the currently approved product information for a medicinal product, such as the SmPC and package leaflet. Promotional elements, either direct or veiled, should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimisation.

Any educational programme should be completely separated from promotional activities and contact information of physicians or patients gathered through educational programmes should not be used for promotional activities.

The educational tools described below can be considered individually or in combinations while developing an educational programme for the purpose of additional risk minimisation.

XVI.B.2.1.1. Educational tools

An educational tool should have a clearly defined scope and should include unambiguous statement(s) regarding the risk(s) of concern to be addressed with the proposed tool, the nature of such risk(s) and the specific steps to be taken by healthcare professionals and/or patients in order to minimise those risks. This information should focus on clearly defined actions related to specific safety concerns in the risk minimisation plan and should not be unnecessarily diluted by including information that is not immediately relevant to the safety concern and that is adequately presented in the SmPC or package leaflet. In addition to an introductory statement that the educational material is mandatory as a condition of the marketing authorisation in order to further minimise important selected risks, elements for inclusion in an educational tool could provide:

- guidance on prescribing, including patient selection, testing and monitoring, in order to minimise important selected risks;
- guidance on the management of such risks (to healthcare professionals and patients or carers);
- guidance on how and where to report adverse reaction of special interest.

Further guidance on the responsibilities of the applicant or marketing authorisation holder and the competent authorities are provided in XVI.C.1..

XVI.B.2.1.1.1 Educational tools targeting healthcare professionals

The aim of any educational tool targeting a healthcare professional should be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (how to manage adverse reactions) associated with the medicine and the specific risks needing additional risk minimisation measures, including:

- selection of patients;
- treatment management such as dosage, testing and monitoring;
- special administration procedures, or the dispensing of a medicinal product;
- details of information which needs to be given to patients.

The format of a particular tool will depend upon the message to be delivered. For example (indicative), where a number of actions are needed before writing a prescription for an individual patient, a checklist may be the most suitable format. A brochure may be more appropriate to enhance

awareness of specific risks with a focus on the early recognition and management of adverse reactions, while posters for display in certain clinical environments can include helpful treatment or dosage reference guides. Other formats may be preferable, depending on the scope of the tool.

XVI.B.2.1.1.2. Educational tools targeting patients and/or carers

The aim of patient targeted tools should be to enhance the awareness of patients or their carers on the signs and symptoms relevant to the early recognition of specific adverse reactions causing the need for additional risk minimisation measures and on the best course of action to be taken should any of those symptoms occur. If appropriate, a patient's educational tool could be used to provide information and to remind the patient about an important activity, for example a diary for posology or diagnostic procedures that need to be recorded or conducted by the patient and eventually discussed with healthcare professionals, to ensure that any steps required for the effective use of the product are adhered to.

Patient alert card

The aim of this tool should be to ensure that special information regarding the patient's current therapy and its risks (e.g. potential interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate. The information should be kept to the minimum necessary to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including emergency. Portability should be a key feature of this tool.

XVI.B.2.2 Controlled access programme

A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures i.e. legal status. Controlled access should be considered as a tool for minimising a serious risk for a product with clearly demonstrated benefits but which would not be available without additional risk minimisation measure(s) due to the public health impact of the risk.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination):

- specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria;
- prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product;
- explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry;
- medicines made available for dispensing only to Pharmacies who are registered and approved to dispense the product.

On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example, monitoring of the patient's health status, laboratory values or other characteristic (e.g. an ECG) prior to and/or during treatment, e.g. liver function tests, regular blood tests, pregnancy test (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SmPC where this is critical to risk-benefit balance of the product.

Since a controlled access programme has large implications for all stakeholders, the use of such a programme is likely to be driven by therapeutic need for the product based on its demonstrated benefit and the nature of the risk.

XVI.B.2.3. Other risk minimisation measures

XVI.B.2.3.1 Pregnancy prevention programme

A pregnancy prevention programme (PPP) is a set of interventions aiming to minimise pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects. The scope of such a programme is to ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It could also target male patients in case use of a medicinal product by the biological father might have a negative effect on pregnancy outcome.

A PPP combines the use of educational tools to control appropriately access to the medicine. Therefore, the following elements should be considered individually and in combination in the planning of a PPP:

- educational tools targeting healthcare professionals and patients to inform on the teratogenic risk and required actions to minimise this risk e.g. guidance on the need to use more than one method of contraception and guidance on different types of contraceptives; information included for the patient on how long to avoid pregnancy after treatment is stopped;
- controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescription or dispensing of the medicinal product (and);
- prescription limited to a maximum of 30 days supply;
- monitoring of the programme performance;
- counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.

The design and implementation of a pregnancy registry should also be considered for universal enrolment of patients who become pregnant during treatment or within an appropriate time from the end of treatment e.g. 3 months.

XVI.B.2.3.2 Direct health care professional communication (DHPC)

A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices to minimise particular risks and/or to reduce the burden of adverse reactions with a medicinal product (see Module XV).

XVI.B.3. Implementation of risk minimisation measures

Additional risk minimisation measures can consist of one or more interventions that should be implemented in a sustainable way to a defined target audience. Careful consideration should be given to both the timing of any intervention and the procedures to reach the target population. For example, a one-off distribution of educational tools 'before launch' may be insufficient to ensure that all potential prescribers and/or users, including new prescribers and users, are reached. Additional periodic re-distribution of the tools after launch might be necessary. Careful consideration should be given to the

layout of the educational tools to ensure a clear distinction from any promotional material distributed. Submission of educational material for review by the national competent authority should be separate from submission of promotional material and a covering letter should clearly state whether the materials are promotional or educational. Furthermore, educational tools should be distributed separately from promotional materials as a 'stand-alone' communication and it should be clearly stated that the tools are not promotional material. Quality assurance mechanisms should ensure that the distribution systems in place are fit for purpose and auditable.

XVI.B.4. Effectiveness of risk minimisation measures

Evaluating the effectiveness of risk minimisation measures is necessary to establish whether an intervention has been effective or not, and if not then why the intervention was not succesful and whether corrective actions are necessary. The evaluation should be performed for the risk minimisation tools individually and for the risk minimisation programme as a whole.

The evaluation should address different aspects of the risk minimisation, the process itself (i.e. to what extent the programme has been implemented as planned), its impact on knowledge and behavioral changes in the target population, and the outcome (i.e. to what extent the predefined objectives of risk minimisation were met, in the short and long term). The time of assessing each aspect of the intervention should also be carefully planned within the RMP prior to initiation.

To evaluate the effectiveness of risk minimisation measures two indicators should be considered:

- process indicators;
- outcome indicators.

Process indicators are necessary to gather evidence that the implementing steps of risk minimisation measures have been successful. These process indicators should provide insight into what extent the programme has been executed as planned and whether the intended impacts on behaviour have been observed. Implementation metrics should be identified in advance and tracked over time. The knowledge gained may be used to support corrective implementation action as needed. Assessing the implementation process can also improve understanding of the process(es) and causal mechanism(s) whereby the additional risk minimisation measure(s) did or did not lead, to the desired control of specified risks.

Outcome indicators provide an overall measure of the level of risk control that has been achieved with a risk minimisation measure. For example, where the objective of the intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.

The conclusion of the evaluation may be that risk minimisation should remain unchanged or modifications are to be made to existing activities. Alternatively, the assessment could indicate that risk minimisation is insufficient and should be strengthened (e.g. through amendment of warnings or recommendations in the SmPC or package leaflet, improving the clarity of the risk minimisation advice and/or by adding additional tools or improving existing tools). Another decision may be that the risk minimsation is disproportionate or lacking a clear focus and could be reduced or simplified (e.g. by decreasing the number of tools or frequency of intervention).

In addition to assessing the effectiveness of risk minimisation measures in managing safety concerns, it is also important to assess if the risk minimisation intervention may have had unintended (negative) consequences relevant to the public health question under consideration, either in the short and/or long term.

The legislation defines “Any study ….measuring the effectiveness of risk management measures” as a post-authorisation safety study [DIR Art 1 (15)). Therefore, the detailed guidance for conducting a post-authorisation safety study, which is provided in Module VIII, should be followed. The ENCePP Guide on Methodological Standards in Pharmacoepidemiology[1] should be considered as appropriate.

XVI.B.4.1. Process indicators

Process indicators are measures of the extent of implementation of the original plan, and/or variations in its delivery. Process indicators should complement but not replace the assessment of the attainment of the objectives aimed at by the risk minimisation measures (i.e. outcome indicators). Depending on the nature of the interventions various process indicators can be identified for the assessment of their performance.

XVI.B.4.1.1 Reaching the target population

When risk minimisation measures involve the provision of information and guidance to healthcare professionals and/or patients by mean of educational tools, measures of distribution should be used to acquire basic information on implementation. These metrics should focus on the appropriateness of the tool for the target audience (e.g. adeguate language, pictures, diagrammes or other graphical support) or assess whether the materials were actually received by the target population.

XVI.B.4.1.2 Assessing clinical knowledge

In order to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision (for example via the SmPC), scientifically rigorous survey methods should be applied. Appendix I at the end of this Module summarises key methodological aspects to be considered for the design and implementation of a survey.

A survey generally includes a core of standard questions administered through telephone contact, in person interview, or self-administered through postal/electronic communication, which are repeated over time. Such an approach may be tailored to the monitoring of attitude and knowledge in representative populations of healthcare professionals and/or patients by means of appropriate psychometric measures. A randomised sample and an adequate sample size should be selected.

Appropriate attention should be given to the research objectives, study design, sample size and representativeness, operational definition of dependent and independent variables, and statistical analysis. Thorough consideration should also be given to the choice of the most appropriate data collection instruments (e.g. questionnaires).

XVI.B.4.1.3 Assessing clinical actions

In order to evaluate the effectiveness of educational interventions and/or information provisions, not only clinical knowledge but also the resulting clinical actions (i.e. prescribing behaviour) should be measured. Drug utilisation studies by means of secondary use of electronic records should be considered as a valuable tool to quantify clinical actions, if representative of the target population. The analysis of prescription records, especially when linked to other records of patients (e.g. clinical and demographic data), may allow the evaluation of prescribing behaviour, including co-prescribing of two interacting medicinal products, compliance with laboratory monitoring recommendations, as well as patient selection and monitoring. By applying appropriate statistical methods (e.g. time series analyses, survival analyses, logistic regression) to a cohort of medicines users, different aspects of

[1] http://www.encepp.eu

prescribing or use may be assessed, which can provide insights beyond purely descriptive evidence. Careful consideration should be given to the conduct and interpretation of drug utilisation studies across European countries, including the legal status of the medicine and how it is prescribed and dispensed, since prescription patterns may reflect not only the product information and any risk minimisation intervention, but also national guidelines, aspects related to healthcare services and reimbursment constraints.

The study of behaviour based on data collected through surveys should be considered when no pre-existing resources and data are available to evaluate clinical actions (i.e. conduct a drug utilisation study based on self-reported data collected in healthcare professionals and/or patients survey).

XVI.B.4.2. Outcome indicators

The ultimate measures of success of a risk minimisation programme are the safety outcomes, i.e. the frequency and/or severity of adverse reactions in relation to patients' exposure to the medicine outside of an interventional study setting (i.e. non-interventional setting) and those safety outcomes should be the outcome indicator(s). Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency such as incidence rate or cumulative incidence of an adverse reaction, obtained in the context of post-authorisation safety studies. Under any approach, scientific rigour and recognised principles of epidemiologic research should always guide the assessment of the final outcome indicator of interest. Comparisons of frequency before and after the implementation of the risk minimisation measures (i.e. pre-post design) should be considered. When a pre-post design is unfeasible (e.g. risk minimisation measures are put in place at the time of initial marketing authorisation), the comparison of an outcome frequency indicator obtained post-intervention against a predefined reference value obtained from literature review, historical data, expected frequency in general population, would be acceptable (i.e. observed versus expected analysis) and should take into account any stimulated reporting. The selection of any particular reference group should be appropriately justified.

Spontaneous reporting rates (i.e. number of suspected adverse reaction reports over a fixed time period) should not be considered as an acceptable estimate of the frequency of adverse events in the treated population, except in very specific circumstances, for instance when there is a negligible background incidence of the adverse event in the general population and a strong association between treatment and the adverse event. In those circumstances when a direct measure on the risk in the treated population is not feasible, spontaneous reporting could offer an approximation of the frequency of the adverse reaction in the treated population, provided that some reasonably valid data can be obtained to evaluate the reporting rate in the context of a product use. However, the well know biases that affects reporting of suspected adverse reaction may provide misleading results. For instance, the introduction of a risk minimisation plan in response to a safety issue detected in the post-authorisation phase of a medicinal product may raise awareness regarding selected adverse reactions which ultimately may result in an increased reporting rate. In these circumstances an analysis of spontaneous reporting may mislead to the erroneous conclusion that the intervention was ineffective. Decreasing reporting rates over time may also lead to the erroneous conclusion that the intervention was effective.

XVI.B.5. Coordination

If several products, including medicinal products authorised according to art. 10(1) or 10(3) (herein referred to as "generics" or "hybrids", as appropriate), of the same active substance are available in a market there should be a consistent approach in the use of additional risk minimisation measures overseen by the national competent authorities. When a coordinated action for a class of products is

needed a harmonised approach should be agreed if appropriate. Under these circumstances advanced planning should ensure that the effectiveness of risk minimisation measures (see XVI.B.4) can be considered for each individual product as well as for the products collectively.

XVI.B.6. Quality systems of risk minimisation measures

Although many experts may be involved in developing and implementing risk minimisation measures, the final responsibility for the quality, accuracy and scientific integrity of those measures and the plan describing them lies with the marketing authorisation holder and its qualified person responsible for pharmacovigilance in the EU (QPPV).

The marketing authorisation holder is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in Module I. Tracked versions of the RMP should be submitted to facilitate regulatory assessment. These records, the RMP and the associated risk management systems, as well as any documents on risk minimisation measures may be subject to audit or inspection.

The marketing authorisation holder should ensure appropriate version control of the risk minimisation tools in order to ensure that all healthcare professionals and patients receive up-to-date risk minimisation tools in a timely manner and that the tools in circulation are consistent with the approved product information. To this purpose the market authorisation holders are encouraged to keep track of recipients of any risk minimisation tools. These records may be subject to audit and inspection.

The marketing authorisation holder should ensure that mechanisms for reporting the results of studies or analyses for evaluation of the effectiveness of risk minimisation measures are documented. These may be subject to audit or inspection.

XVI.C. Operation of the EU regulatory network

For centrally authorised products additional risk minimisation measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) and agreed by the Committee for Medicinal Products for Human Use (CHMP) will become, once agreed by the European Commission, conditions for the safe and effective use of a medicinal product.

Implementation of additional risk minimisation measures takes place at national level and allows Member States to tailor the required conditions and restrictions to any national legal requirements and local healthcare systems.

Annex II of the CHMP opinion will outline the key elements of any additional risk minimisation measures imposed on the applicant or marketing authorisation holder as a condition for the safe and effective use of a medicinal product. An annex related to Article 127a of DIR may describe the responsibilities of national competent authorities in ensuring that the additional risk minimisation measures are implemented in the Member States in accordance with defined key elements. Further details or key elements on any additional risk minimisation measures may be included in annex 10 of the RMP (see Module V).

XVI.C.1. Roles and responsibilities in the EU for implementing additional risk minimisation measures

This Section outlines the responsibilities of different bodies as having clear obligations. This includes the Agency and its PRAC, national competent authorities, and the applicant or marketing authorisation holder in the process of developing, implementing and evaluating additional risk minimisation measures introduced for the safe and effective use of a medicinal product in the EU.

In order to respect the diversity of EU health care systems, key elements will be agreed at EU level, which need to be implemented in a coordinated manner across the Member States while providing for agreement of the detail of local implementation at national level. In circumstances where some key elements are specific for only some Member States or where additional risk minimisation measures are not imposed as a condition for marketing authorisation these are included in the RMP.

XVI.C.1.1.The European Regulatory Network

XVI.C.1.1.1 The European Medicines Agency

The Agency shall, in collaboration with the Member States and facilitated through the PRAC, monitor the outcome of risk minimisation measures contained in RMPs and of conditions referred to in points (c), (ca), (cb) and (cc) of Article 9(4) or in points (a) and (b) of Article 10a(1), and in Article 14(7) and (8) of Regulation (EC) No 726/2004 [REG Art 28a(1)(a)].

In monitoring the outcome of risk minimisation measures, the Agency should support the PRAC scientific assessment of the outcome of risk minimisation measures which comprise additional risk minimisation measures, through the integration of data provided by Member State resources and research activities. The PRAC will make recommendations to the CHMP or the Coordination Group – Human (CMDh) as appropriate regarding any necessary regulatory action.

XVI.C.1.1.2. The Pharmacovigilance Risk Assessment Committee (PRAC)

The PRAC should evaluate the outcome of risk minimisation measures, including additional risk minimisation measures and make recommendations as appropriate regarding any necessary regulatory action.

PRAC will normally assess both protocol and results of post-authorisation safety studies which aim to evaluate the effectiveness of risk minimisation measures (see Module VIII).

XVI.C.1.1.3. Competent authorities in Member States

The national competent authorities are responsible for the oversight at national level of the implementation of additional risk minimisation measures imposed as a condition of the marketing authorisation for the safe and effective use of a medicinal product in the EU, irrespective of the route of marketing authorisation.

For those risk minimisation measures introduced after the initial marketing authorisation, the national competent authorities should ensure prompt consideration and agreement with the marketing authorisation holder.

The national competent authorities assisted by the PRAC and CHMP or CMDh, as appropriate, may facilitate harmonising the implementation of risk minimisation tools for generic products of the same active substance. When additional risk minimisation measures are considered necessary for generic medicinal product(s) based on safety concerns related to the active substance, the risk minimisation measures applicable to the generic product(s) should be aligned with those for the reference medicinal product.

Additional risk minimisation measures for hybrid products may be required in some circumstances beyond those of the reference medicinal product (e.g. different formulation or route of administration or incompatibility issues). To facilitate this alignment, the PRAC may give advice on the key elements that should be implemented for all concerned nationally authorised products (as conditions of their

marketing authorisation) and on agreement, may make these general requirements publicly available to facilitate harmonised implementation at national level.

In addition to the above, for centrally authorised products the responsibility of the national competent authorities in ensuring implementation of the risk minimisation measures as addressed to them by the European Commission decision may be outlined in the annex related to Article 127a of DIR. In the absence of such an annex, the general responsibilities of supervisory authorities will apply.

The national competent authorities should ensure that any risk minimisation tool is implemented in line with the key elements outlined in the annex related to Article 127a of DIR. Additionally, the national competent authorities should agree the format and media of the risk minimisation tools, including printed material, web-based platforms and other audio-video media, as well as the schedule planning on interventions with the applicant or marketing authorisation holder before a product is introduced to their market or at any time thereafter as needed.

The national competent authority is autonomous in deciding appropriate national educational materials and/or other risk minimisation tools as long as these are aligned with the key elements agreed at EU level and as outlined in the RMP.

National competent authorities in collaboration with the Agency facilitated through the PRAC shall monitor at national level the outcome of risk minimisation measures contained in RMPs and of the conditions referred to in Articles 21a, 22 or 22a of DIR [DIR Art 107h(1)(a)].

XVI.C.1.2. Marketing authorisation applicant or holder

The applicant or marketing authorisation holder should clearly define the objectives of any proposed additional risk minimisation measure and the indicators to assess their effectiveness. Any additional risk minimisation intervention should be developed in accordance with the general principles outlined in XVI.B.1. and XVI.B.2. and should be fully documented in the risk minimisation plan (see Module V).

The measures adopted in the risk minimisation plan should be implemented at national level after agreement with the national competent authorities.

The applicant or marketing authorisation holder should provide information regarding the status of implementation of additional risk minimisation measures as agreed with the national competent authorities and keep them informed of any changes, challenges or issues encountered in the implementation of the additional risk minimisation measures. Any relevant changes to the implementation of the tools should be agreed with the national competent authorities before implementation.

In the implementation of web-based tools the applicant or marketing authorisation holder should apply requirements specific for each Member State, with particular consideration of potential issues linked to accessibility, recognisability, responsibility, and privacy and data protection.

For generic products the applicant or marketing authorisation holder should develop risk minimisation in line with the scope, content, and format of the tools used for the reference medicinal product. Scheduling and planning of interventions should be carefully coordinated in order to minimise the burden on the healthcare systems.

For generic products, the effectiveness of risk minimisation measures should be assessed by the marketing authorisation holders in close cooperation with the competent authorities. Where formal studies are justified, joint studies are strongly encouraged in order to minimise the burden on the healthcare systems. For instance, if a prospective cohort study is instituted, study entry should be independent from the prescription of a product with a specific invented name or marketing

authorisation holder. Recording of specific product details would still be important to enable rapid identification of any new safety hazard with a particular product.

The marketing authorisation holder shall monitor the outcome of risk minimisation measures which are contained in the RMP or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a of DIR [DIR Art 104(3)(d)]. General principles for effectiveness evaluation are provided in XVI.B.3..

The applicant or marketing authorisation holder should report the evaluation of the impact of additional risk minimisation activities when updating the RMP (see V.B.11.4.).

The applicant or marketing authorisation holder should report in the Periodic Safety Update Report (PSUR) results of the assessment of the effectiveness of risk minimisation measures relevant to the risk-benefit assessment (see VII.B.5.16.5.).

The applicant or marketing authorisation holder should ensure timely communication with the competent authorities for relevant regulatory evaluation and actions, as appropriate (see also XVI.C.2. and Modules V and VII).

XVI.C.1.3. Healthcare professionals and patients

Healthcare professionals and patients hold no legal obligations with respect to the implementation of the pharmacovigilance legislation. Nonetheless the cooperation of healthcare professionals and patients is paramount to the success of educational programmes and/or controlled access programmes in order to optimise the risk-benefit balance. It is desirable that they give careful consideration to any risk minimisation measure which may be introduced for the safe and effective use of medicines.

XVI.C.2. Impact of risk minimisation measures effectiveness on RMP/PSUR

PSUR and RMP updates should include a summary evaluation of the outcome of specific risk minimisation measures implemented to mitigate important risks in the EU. In the RMP, the focus should be on how this informs risk minimisation and/or pharmacovigilance planning. In the PSUR, there should also be evaluation of how the implemented measures impact on the safety profile and/or risk-benefit balance of the product. In general, the focus should be on information which has emerged during the reporting period or since implementation of the most recent risk minimisation measure(s) in the EU. Where there is parallel submission of a PSUR and a RMP update, the use of a common module may be considered (see Modules V and VII).

Results of the assessment(s) of the effectiveness of risk minimisation measures should always be included in the RMP. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation measures. This critical analysis may include reference to experience outside the EU, when relevant.

The evaluation of the effectiveness of risk minimisation measures should focus on whether these have succeeded in minimising risk. This should be analysed using a combination of process and outcome indicators, as described in XVI.B.3.. It may be appropriate to distinguish between risk minimisation measures implemented at the time of initial marketing authorisation and those introduced later in the post-authorisation phase.

When presenting the evaluation of the effectiveness of a risk minimisation measure, the following aspects should be considered:

- The evaluation should provide context by a) briefly describing the implemented risk minimisation measure(s), b) defining their objective(s), and c) outlining the selected process and outcome indicators.
- The evaluation should incorporate relevant analyses of the nature of the adverse reaction(s) including its severity and preventability. Where appropriate logistical factors which may impact on clinical delivery of the risk minimisation measure should also be included.
- The evaluation should include an examination of the delivery of the risk minimisation measures in routine clinical practice, including any deviation from the original plan. Such an evaluation may include the results of drug utilisation studies.
- Outcome indicators (i.e. adverse reaction frequency and/or severity) should normally be the key endpoint when assessing the attainment of risk minimisation measures objectives.

Proposals for changes to enhance risk management should be presented in the regional section of the PSUR. The risk minimisation plan should be updated to take account of emerging information on the effectiveness of risk minimisation measures.

In general, generic products are exempt from routine PSUR reporting. The frequency of RMP updates should be proportionate to the risks of the product. In general, the focus of RMP updates should be on the risk minimisation plan and in providing updates on the implementation of risk minimisation measures where applicable. Where a limited number of modules have been updated, the impacted modules should be clearly highlighted in the cover letter to the submission. If there is a consequential change to the summary RMP, this should also be highlighted in the cover letter. Changes to the product information should not be proposed via a standalone RMP update but rather a variation application should be submitted and the proposed changes captured in the PSUR (if PSURs are being submitted by the MAH for a given generic product).

XVI.C.3. Transparency

Procedures should be in place to ensure full transparency of relevant information pertaining to the risk minimisation measures in place for the concerned medicinal products.

In accordance with Article 106 of Directive 2001/83/EC and Article 26 of Regulation (EC) No 726/2004, the Agency and national competent authorities shall make publicly available public assessment reports for medicinal products, as well as summaries of RMPs (Commission Implementing Regulation (EU) No 520/2012, [IR Art 31], including risk minimisation measures therein described.

For centrally authorised products the Agency shall make public:

- a summary of the risk management plan [REG Art 26(1)(c)], with specific focus on risk minimisation activities described therein [IR Art 31.1];
- the European Public Assessment Report (EPAR) that includes any conditions of the marketing authorisation, such as additional risk minimisation measures [REG Art 26(1)(j)].

By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

- public assessment report; this shall include a summary written in a manner that is understandable to the public [DIR Art 21(4), Art 106(a)];
- summary of product characteristics and package leaflets [DIR Art 21(3), Art 106(b)];

- conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions [DIR Art 21(3)];
- summaries of risk management plans [DIR Art 106(c)]; with specific focus on risk minimisation activities described therein [IR Art 31.1].

To promote public health, it is recommended that the Agency and the national competent authorities make the following information available via their websites:

- details of risk minimisation measures required as a condition of the marketing authorisation (e.g. when risk communication tools consist of printed material, a copy is provided or whenever possible, provision of electronic access to the educational material, patient card, check lists or other risk minimisation tools is advised);
- details of disease or substance registries requested as part of a restricted distribution system.

XVI.Appendix 1. Key elements of survey methodology

Surveys are cross-sectional studies involving primary data collection form individual participants.

In the context of the evaluation of the effectiveness of risk minimisation measures a survey can be conducted to evaluate understanding, knowledge and behaviour resulting from educational interventions in a specified target population with respect to the safety and risk management of a medicinal product.

The survey methodology might not be the most appropriate approach for the evaluation of behaviour, since surveys collect and analyse self-reported data from healthcare professionals and patients. Furthermore participation in a survey in itself may introduce behaviour changes or may not be representative of the target users given that participation is more likely amongst engaged healthcare professionals and/or more health conscious patients.

At a minimum the following elements should be considered in the design and implementation of a survey in order to minimise potential biases and to optimise the generalisability of the results to the intended population:

1. Sampling procedures and recruitment strategy;
2. Design and administration of the data collection instrument (s);
3. Analytical approaches;
4. Ethics, privacy and overall feasibility of a study.

XVI.App1.1. Sampling procedures and recruitment strategy

In any survey, the sampling frame and recruitment of participants may be subject to selection bias leading to a study population that is not similar to, or representative of, the intended population in one or more aspects. Furthermore, it should be considered that a selection bias cannot be removed by an increase of the sample frame, the sample size or the response rate. Key elements to be considered in the sampling frame include age, gender, geographical distribution, and additional characteristics of the study population. For instance, the sampling approach for a physician's survey should consider specialty, type of practice (e.g. primary care, specialist ward, academic institution), length of professional experience, frequency of prescribing the product of interest and ideally should be randomised. In a patient's survey income and education, medical condition(s), chronic vs acute use, should be accounted for.

In addition to the overall representativeness of the target population the recruitment strategy of a survey should give careful consideration of the potential recruitment sources. For the recruitment of healthcare professionals, sponsor lists, web panels, professional and learned societies may represent a feasible approach. However, their representativeness for the intended target population of physicians needs to be carefully reviewed for each study. For patient recruitment the relevant clinical setting, existing web-panels, and patient advocacy groups should be considered. A recruitment strategy should be designed while accounting for the chances of achieving accurate and complete data collection. Efforts should be made to document the proportion of non-responders and their characteristics to evaluate potential influences on the representativeness of the sample.

XVI.App1.2. Design and administration of the data collection instrument (s)

Data collection approaches in a survey may vary from in-person interview, testing, and measurement or collection of biological samples as for routine clinical practice, to telephone interview, web-based or

paper-based questionnaires, audio computer-assisted self-interviewing (A-CASI), interactive voice response systems (IVRS), or mixed mode approaches are also appropriate. The choice of the most suitable data collection approach will depend on the target population characteristics, the disease and the treatment characteristics and the inclusion and exclusion criteria of the study.

Each data collection approach will require the ad hoc design of one or more specific instruments. Nonetheless general design considerations that may apply to all instruments include the following:

- burden to participant: e.g. length or duration, cognitive burden, sensitivity to participant;
- clarity and sequence of questions: e.g. use of unambiguous language, minimising assumptions, starting with the most important questions and leaving sensitive questions until later;
- completeness of responses: e.g. structure questions in order to lead to a single unambiguous answer, allow for choices such as “unknown” or “don’t know”;
- layout of data collection instrument: e.g. clear flow, technology-assisted guides (avoid patterns, reminders for non-response and visual images);
- testing and revision of instrument: e.g. formal testing using cognitive pre-testing such as one-to-one interviews, probing questions, interview guide or trained interviewer, and “think aloud” process;
- incentives to improve response rate: e.g. aggregated data are fed back to the participants.

XVI.App1.3. Analytical approaches

The key analytical elements of a survey should include:

- descriptive statistics, such as:
  - the percentage of participants responding correctly to knowledge questions;
  - stratification by selected variable;
  - data on no response or incomplete response.
- comparison of responders and non-responders characteristics.
- comparison of responders and overall target population characteristics.

When survey results are weighted, the following key points should be considered:

- differences in selection probabilities (e.g. if certain subgroups were over-sampled).
- differences in response rates.
- post-stratification weighting to the external population.
- clustering.

Examples of stratified analyses include the following:

- specialty of physician;
- geographic location;
- receipt of any educational material;
- volume of prescribing.

XVI.App1.4. Ethics, privacy and overall study feasibility

Ethical requirements are not harmonised across EU Member States, with notable differences in national (or regional) processes.

The overall feasibility assessment of a study is a key step in the successful implementation of a survey. Key elements of such an assessment include:

- gathering information on site and characteristics of study population (patients or healthcare professionals);
- estimating reasonable study sample size, the number of sites required to achieve the sample size, and approximate length of the data collection period (e.g. based on estimated patient volume, frequency of patient visits, and expected patient response rate);
- evaluating site resources and interest in the study.