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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

REFLECTION PAPER ON RISK MANAGEMENT PLANS FOR CENTRALLY AUTHORISED VETERINARY MEDICINAL PRODUCTS

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REFLECTION PAPER ON RISK MANAGEMENT PLANS FOR CENTRALLY AUTHORISED VETERINARY MEDICINAL PRODUCTS

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1. INTRODUCTION (BACKGROUND)

The current legislation foresees that the applicant may need to develop and describe in detail a risk management system for inclusion in the application before a marketing authorisation can be granted for a medicinal product for veterinary use.

Article 31(1) of Regulation (EC) 726/2004 (Ref. 1) refers to Art 12(3) of Directive (No) 2001/82/EC, as amended (Ref. 2), that sets the requirement for a risk management system stating that the application for a marketing authorisation shall contain, in particular, the following information...

> (k) *a detailed description of the pharmacovigilance system, and, where appropriate, the risk management system that the applicant will put in place.*

Veterinary pharmacovigilance is in continuous development. The provision for risk management systems is new in the field of veterinary medicines and therefore gives opportunity for novel, targeted and risk-based approaches to take place in the monitoring and management of safety of authorised medicinal products for veterinary use, as appropriate. The legal provision for risk management plans (RMPs) was originally developed in response to safety issues arising from the use of human medicinal products and Marketing Authorisation Holders (MAHs) of medicinal products for human use are now required to submit RMPs as a routine part of all marketing authorisation applications. The situation is not the same with respect to veterinary medicines. the need for RMPs is less evident in the absence of major post authorisation safety issues. For this reason profound and critical considerations are, however, needed prior to implementation of the legal provision to benefit all involved stakeholders including the applicants, Marketing Authorisation Holders, the competent authorities in the EU Regulatory Network and the general public.

2. DISCUSSION

The risk management system is intended to become a systematic tool for providing data on risks and solutions for controlling those risks. Such data are intended for considerations and maintenance of the benefit-risk balance of products, when appropriate (Ref. 3).

The following elements of the risk management system need consideration and establishment:

1. the definition of the risk management system,
2. the scope, and the risk types that this system is designed to address,
3. the expected contents of the description of the risk management system (risk management plan),
4. the initiation, practical submission, maintenance and termination of the risk management plan,
5. communication.

<u>Definition and scope of a Risk Management System</u>

The risk management system would be defined as

> *a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of effectiveness of those interventions.*

While this definition would thereby be identical for medicinal products for veterinary and human use (Ref. 4), the practical implementation should consider the particularities of veterinary medicines.

Scope

Experience on effective pharmacovigilance activities is continuously gained throughout the European Community. Information on the functioning of the system is, however, scattered. CVMP considers that it is appropriate, at least initially to limit the scope to very special products for which the need for special arrangements is obvious, i.e. situations where there are identified *potential or actual risks* that cannot be managed through routine pharmacovigilance. These situations might most often be related to products with certain types of risks, e.g. known user safety risks or risks to the environment, or to products authorised under exceptional circumstances). Based on experience to be gained with this limited subset of products and on further developments with respect to pharmacovigilance in general, consideration will be given at a later date to the scope of products requiring risk management plans.

The *potential or actual risks* leading to the need for a risk management system would, however, need to be clarified in detail.

Existing guidelines (Ref. 5) and additional CVMP Recommendations should be used as far as possible for planning and executing the targeted pharmacovigilance activities.

Experiences with the use of risk management systems should be systematically collected by the CVMP to evaluate the effect and value of the recommendations concerning risk management systems.

Suggested contents of the description of the risk management system (risk management plan)

The following elements describe four parts of a possible risk management plan:

1. Identify known and potential risks whether product or class-related, as well as areas lacking data and conclude on the existence of *specific* safety issues (Safety Specification):

   The approved SPC serves as a reference document - a safety specification – in signal detection on e.g. PSUR data. The SPC is, however, limited to the information on known risks (animal adverse reactions and human reactions, environmental effects) and agreed risk management measures (e.g. contraindications, precautions for use). For future signal detection for veterinary medicinal products, discussions on the use of an extended safety specification have been initiated. This safety specification would collect and summarise information on risks not only from the approved SPC but also from other documents relevant to the marketing authorisation.

2. Define those specific activities that complement routine pharmacovigilance and that address the *specific* safety issues, if any (Pharmacovigilance Plan):

   For veterinary medicinal products, the pharmacovigilance plan could be limited to statements on the need for collection of specific data from targeted groups of animals for instance in post-marketing surveillance studies conducted by the marketing authorisation holder on basis of the opportunity given by legislation[1]. The collection may be triggered on the basis of the guideline on a strategy for triggering pharmacovigilance investigations preceding regulatory actions by EU competent authorities (Ref. 6). The collection could be guided by the guideline for the conduct of post-marketing surveillance studies of veterinary medicinal products (Ref. 7).

3. Evaluate the need for risk minimisation activities for each specific safety issue:

   An evaluation of the need for risk minimisation activities is usually already done by the applicant during the development process prior to initial authorisation. For instance, the final proposed formulation and packaging, as well as the proposed product literature and

[1] In accordance with Art 51 of Regulation EC (No) 726/2004, for a period of five years following the initial placing on the market in the Community, the Agency may request on justified grounds that the MAH arrange for specific pharmacovigilance data to be collected from targeted groups of animals.

prescription status already reflect minimisation actions taken. At the time of authorisation any outstanding issues should be listed and additional risk minimisation activities proposed to be taken if post-authorisation experience confirms the risk to be a matter where more guidance, communication or other minimisation actions are needed.

4. Identify needed risk minimisation actions, and their objectives (Risk Minimisation Plan), if needed.

A template would need to be developed for applicants and Marketing Authorisation Holders to harmonise submission of risk management plans and facilitate their assessment by competent authorities.

Initiation, submission, evaluation and termination of risk management plans

A product might become subject to the need for a risk management plan at any time throughout its life cycle.

A risk management plan may be provided with the initial marketing authorisation application or when significant changes to the marketing authorisation are applied for if any *potential or actual risks* are identified by the applicant.

In addition, requests for the provision or amendment of a risk management plan could be made on justified grounds during any procedure and in conjunction with assessment of pharmacovigilance data by the CVMP, if relevant risks emerge. The CVMP would decide on the acceptability of a provided risk management plan or whether such a plan is necessary, as applicable.

Risk management plans would be assessed when submitted and would contribute to the evaluation of the benefit-risk balance of the product. A delegation of assessment could be considered to ensure harmonisation, involving the CVMP Pharmacovigilance Working Party, in accordance with its given mandate (Ref.8).

The safety data and other information emerging from the actions described in a risk management plan would be assessed by the CVMP or, as appropriate, its Pharmacovigilance Working Party.

Existing risk management plans would be maintained and updated versions submitted in synchrony with PSURs.

A summary of conclusions would be prepared on a yearly basis by the CVMP as part of the benefit-risk evaluation in the annual report.

Once actions outlined in the risk management plan have been successfully completed, the plan would be terminated. Emerging risks may, as described above, lead to the development of a new risk management plan for the same product.

Procedures for communication between the competent authorities within the EU regulatory network are already in place to facilitate rapid exchange of information and to enable harmonised, simultaneous action in response to emerging data, as necessary. The Rapid Alert and Non Urgent Information System would frequently be suitable.

Communication

Various aspects need to be considered and agreed concerning communication to the public on the contents of and outcomes stemming from risk management systems for all applicable products. These aspects would best be considered in a wider context covering all pharmacovigilance communication.

3. CONCLUSION

The CVMP agrees on the need to establish a definition and a scope for risk management plans for veterinary medicinal products. There may be a need to provide recommendations to applicants and MAHs on the requirements, initiation, submission, maintenance and termination of detailed descriptions of risk management systems, when appropriate. Following the feedback received on this reflection paper, the CVMP would decide on the need and extent of guidance and the timing for developing such guidance.

The proposed scope is limited to require a risk management plan for products in situations where there are identified potential or actual risks that cannot be managed or mitigated through routine pharmacovigilance, in accordance with criteria to be set or when requested by the relevant competent authority to ensure that the benefit/risk balance becomes or remains positive.

Various aspects on pharmacovigilance communication would best be considered in a separate overall communication plan on veterinary pharmacovigilance.

Experiences would be systematically collected by the CVMP on the use of risk management plans to evaluate the effect and value of these.

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