The new guideline on User Safety of topically applied veterinary medicinal products

The User Safety Guideline for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) provides guidance on how User Safety Risk Assessments (USRA) should be conducted - but no specific guidance on how exposure from topically administered products should be assessed. As well as the risk to those handling and administering them, topically applied veterinary medicinal products (VMPs) pose additional risks to those exposed via contact with a treated animal.

The need for a harmonised approach to user safety
In recent years, the number of topically applied VMPs on the market within the EU has increased. In the absence of a specific guideline, existing guidance from EU Member States and/or methodology utilised by the Environmental Protection Agency (EPA) of the USA have been applied in USRAs submitted for these products. These divergent approaches have in turn led to differing opinion among the competent authorities as to the correct stance to take, causing difficulty during the registration process. Therefore, the initiative to establish a guideline on the user safety of topically administered VMPs was welcomed by the Federation of Veterinarians of Europe (FVE) and Animal Health Europe at the time of the initial consultation back in 2014.

Six years on from the initial concept paper, and the final version has now been adopted (Link), coming into force on November 1st 2018. The adopted guideline provides many valuable clarifications on approaches to user safety risk assessments for topically administered products that can be considered appropriate by the EU Competent Authorities, as well as disambiguation of certain terms used and, quite importantly, the scope of the guideline itself. The existing guidance issued by individual EU Competent Authorities, and the EPA, have been reviewed in generating this guideline.

Companion animal focus and types of VMP considered
The new guideline was created with the intended scope being chiefly companion animals, although the principles within it may apply more widely. Some topically applied products, e.g. pour-ons, are not covered because of this companion animal focus. The initial concept paper may have caused confusion in this regard, since the examples of topically-applied products listed there include pour-ons, and some of the comments received from stakeholders point to the lack of clarity in the wording which make it unclear whether farm animals should fall within the scope of the guideline. The types of products addressed in the document however do include spot-ons, shampoos, and collars.

Exposure scenarios and equations for calculation
Overall, the document contains helpful clarifications on expected exposure scenarios for adults and children via various routes and with varying duration, dependent on the product type. Guidance regarding the selection of appropriate Toxicological Reference Values (TRVs) for all scenarios is provided. Parameters of so-called wipe tests are more clearly described, and the level of detail given on this subject is more in-depth than other sections due to an absence of guidance elsewhere. For products such as collars and shampoos, quantities that may be accidentally swallowed are defined. Possible inhalation exposure to products applied by spray is not addressed, however: it is proposed that this will be assessed on a case-by-case basis. For each scenario, equations are provided which calculate the exposure – the calculations focus on the most sensitive population i.e. children when both adult and children could be exposed, so that additional calculations for adults do not generally have to be provided (the exception being at-risk specific populations e.g. pregnant women).

In addition to the guidance already provided in the general USRA guideline, more detail regarding the quantitative risk assessment is provided. Further, detailed advice regarding suitable risk mitigation measures has been set out.

Extrapolation of data from human medicine

Fuller explanation of the authorities' approach to the use of data from the field of human medicine is also given via the comments document. Applicants and MAHs may previously have assumed that the therapeutic dose established for a licenced human product containing a particular active substance could act as a suitable TRV, where only minor effects have been reported and the anticipated exposure is less than that of therapeutic use in humans. That opinion is not upheld: approval of the human product would have been on the basis of risk : benefit assessments that do not apply when the person exposed is not the patient.

Stakeholder comments not upheld

Items raised by stakeholders in the summary of comments that were not upheld include the position that certain packages are difficult for children to open, and this should be taken into account in estimating risk of exposure even if the package is not 'officially' a child-proof design. Following comments from stakeholders regarding oral exposure scenarios, clarification was provided regarding the maximum amount of products considered unpalatable (i.e. shampoo), or too big to swallow (off-cuts from collars) that could be ingested by a child.

Where the guideline will be applied

It is stated that the applicability of the guideline will not be retrospective – i.e. authorised products will not require any reassessment of user safety in light of the new recommendations. There are some exceptions foreseen, however: changes to the clinical use that result in a significant increase in the dose handled, including duration of use; new information impacting on the existing risk assessment such as new hazard data on the ingredients (including excipients); or change of packaging that results in increased potential for user exposure, particularly change affecting possible spill volumes or child-resistant properties of the pack.

There can be no doubt that there was a strong need to achieve a clear harmonised approach to USRA for topically applied products and therefore this guideline is greatly welcomed.