charles river

Summary
An assessment of environmental safety for veterinary medicinal products (VMPs) has been required as part of the safety submission for a Marketing Authorisation (MA) since 1992.

SAFETY ASSESSMENT

Environmental Impact (Risk) Assessment of Veterinary Medicinal Products

The introduction of active pharmaceutical ingredients (APIs) into the environment via the prescribed use of veterinary medicinal products (VMPs) can potentially endanger the environment. Exposure of the environment can follow administration of an aquaculture treatment or through veterinary treatment of livestock or companion animals.

To assess this impact, submission of an environmental risk assessment (ERA) is included in the authorization process for new and generic VMPs. Within the VICH regions, the risk assessment process and data requirements is harmonized and follows a tiered approach as described in VICH GL 6 (Phase I) and VICH GL 38 (Phase II) and shown in figure 1.

If the results of Phase I show that the environment may be exposed to the API, an impact assessment is carried out in Phase II. The applicant must then provide the authorization body with data on the API's

- **Physicochemical properties**; this data is used to evaluate potential study design adaptations and as input parameters for calculating the predicted environmental concentration (PEC).
- **Ecotoxicological properties**; this data is used to derive predicted no effect concentrations (PNEC) for the potentially exposed compartments.
- **Behavior in the environment**; this data is used to refine the phase I PEC calculation in the potentially exposed compartments. Refinements might require complex exposure calculation models, including FOCUS (groundwater and surface water scenarios).

Based on all available data a quantitative risk assessment using risk quotients (PEC/PNEC ratios) and fixed cut-off points ($\log_{Kow}$, $PEC_{groundwater}$, soil nitrogen transformation) is performed for the relevant environmental compartments; the risk assessment is conducted in a two-stage assessment (Phase IIA/IIB; Phase IIB is triggered based on the Phase IIA outcome). For those compartments where a risk is identified, the need for further data and/or risk mitigation measures will be defined in consultation with the regulatory authority. When the potential environmental risks outweigh the VMP's benefits, the application for authorization of the medicinal product will be denied.

In addition to the VICH guidelines, EMA details further guidance on different aspects of an ERA, including strategies on higher tier plant testing and dung fauna testing. Most impact however is to be expected from the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances. An assessment is performed in Phase I (if the log octanol/water partition coefficient of the API is ≥ 4) or in Phase II, and is primarily hazard-based. The outcome can potentially lead to refusal or restrictions of the marketing authorization. As a result, the use of specific groups of VMPs (e.g., parasiticides) might be endangered and hence the need for effective risk mitigation measures should carefully be evaluated.

As environmental risk assessments required for different regulatory frameworks follow the same scientific principles, Charles River Laboratories' extensive experience in the areas of agrochemicals, biocides and human pharmaceuticals has a significant added value for the ERA service provided for VMPs.

In addition to performing the studies required, we can provide project management and advice during every stage of the program as well as prepare the environmental assessment reports ready for submission to the VICH parties (EMA, FDA and JMAFF).

Figure 1: ERA as described in VICH GL 6 (Phase I) & VICH GL 38 (Phase II)