The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

Position Paper on the establishment of MRLs for milk considering the daily intake by children

1. Background

The approach used by the CVMP for the evaluation of the safety of residues of veterinary medicines is based on the determination of the Acceptable Daily Intake (ADI) for the pharmacologically active substances contained in the veterinary medicines on which MRLs are subsequently based. The ADI is an estimate of the residue, that can be ingested daily over a lifetime without a health risk to the consumer. The ADI may be set on the basis of toxicological, pharmacological or microbiological data: whichever is the lowest. When the ADI is based on toxicological or pharmacological data, the lowest no-observable-effect-level (NOEL) with respect to the most sensitive parameter in the most sensitive test species is identified from a battery of toxicology/pharmacology studies, or in some cases, where such data are available, from observations in humans. Often a safety factor of 100 (10 to correct for intraspecies variability and 10 for interspecies extrapolation) is applied to extrapolate from the NOEL to the ADI, but depending on the relevance and the quality of the available toxicity/pharmacology data, safety factors can range from 10 to 1000.

The relevant residues and in particular the marker residue are identified on the basis of pharmacokinetic and depletion studies.

Consideration is also given to the potential consumer intake of residues by calculating the levels of consumption of residues in foods of animal origin on the basis of arbitrarily high fixed consumption values to ensure the protection of the majority of consumers. The daily food basket used for such consumption calculation is comprised of: 0.500 kg of meat[1] or 0.300 kg of fish plus 1.500 kg milk plus 0.100 kg eggs plus 0.020 kg honey. The estimation of the consumer intake also takes into account the residue concentration in the food commodities derived from the pattern of residue depletion of the substance in the target animal. Where appropriate residues from the pesticide use of a substance are also taken into account.

In summary the determination of MRLs for pharmacologically active substances is based on the ADI, the identified marker residue and total residues, the tissue distribution and the EU food basket. MRLs are established in such a way that the maximum theoretical intake, as calculated from MRLs and food basket does not exceed the ADI.

Once MRLs have been allocated, it is then necessary in the context of granting a marketing authorisation to determine a withdrawal period for such veterinary medicines; this ensures that residues from the authorised use of the product concerned will not exceed the MRLs.

[1] 0.500 kg comprises for mammals 0.300 kg of muscle, 0.100 kg of liver, 0.050 kg of kidney and 0.050 kg of fat (for pigs, fat and skin in natural proportions) and for poultry 0.300 kg of muscle, 0.100 kg of liver, 0.010 kg of kidney and 0.090 kg of fat and skin in natural proportions

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As previously described the theoretical intake is calculated on the basis of the "food basket". The "food basket" is mainly reflecting the dietary pattern of adults. Children might have a different dietary pattern. This is not fully covered by the "food basket". For some compounds where a relatively larger fraction of the ADI is allocated to MRL for milk than to MRLs for meat, this may result in a theoretical risk for children of exceeding the ADI, because they consume relatively more milk and milk derived products than adults.

2. Discussion

The simplest method for the determination of the residue estimate multiplies the maximum residue limit for individual drugs by a fixed value for milk consumption, thereby assuming that all potentially treated milk will contain residues at this level. In practice, this approach would significantly overestimate the exposure in children. An exposure model should account for variability in milk intake between individuals as well as variability in the concentration of residues present in milk. Such model is outlined below. Within the model the main exposure pathway is outlined, influencing factors are described and potential sources of uncertainty are considered.

Risk analysis, including risk management of residues from veterinary medicinal products when setting MRLs refer to the single cow, but in practice it is unusual to consume milk coming from one cow only. The milk is mixed at farm level, and at the dairy where it is mixed with milk from other farms. Residues from veterinary medicinal products in milk at or below the MRL when coming from the single cow are thus further diluted in the farm tank and at the dairy. This approach of collecting and mixing tank milk is also recognised in the respective legislation on monitoring regulations for milk (Commission Decision of 27 October 1997)[2].

3. Relevant factors

Many factors influence the exposure of children to residues of veterinary medicinal products in milk. In estimating the probability of consumption of milk, the variability factors include the child's bodyweight, age, social status, parental choice (breast fed against bottle fed), whether or not a dietary sensitivity to bovine milk proteins is present in the child, whether the child is from a rural or urban household, as well as factors such as the price of cows' milk versus the price of milk replacement products. Factors affecting the uncertainty of the data include the time of the year, the size of the population surveyed to generate the consumption data, as well as any analytical errors in the measurement of the consumption variables.

The variability factors which influence the probability of the milk contains residues are complex. Only some cows receive veterinary medicinal products during their lactation. Factors which predispose an animal to a disease include its genetic make-up, its nutritional status, the husbandry and environmental conditions. The presence and challenge load of an infectious or parasitic agent(s) affects the epidemiological characteristics of a disease. In considering the choice of treatment or preventative measure to limit the disease, several additional factors come into play including the choice of a cost-effective drug, whether the animal is part of a group which requires mass medication, the pharmacodynamic and pharmacokinetic characteristics of the drug and the drug formulation. In establishing withdrawal periods for individual product formulations, regulatory authorities employ conservative means to predict a time period by which residues deplete to concentrations below the permitted maxima. These means include using data sets generated using maximum recommended dosage rates in treated animals and using numbers of cows in various stages of lactation to reflect high and low milk yields. Modern methodology now employs sophisticated statistical tools to increase the confidence in the withdrawal period to the point where, at the end of the withdrawal period, the concentration of the residue of interest is below the limit of quantification in many animals and below the MRL in all test animals.

[2] OJ N° L 303 of 6.11.97

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Other variability factors include the dilution factors with milk from untreated animals within the herd as well as with dilution with pooled milk from untreated herds. Uncertainty factors include the adequacy of treatment records in individual farms which together with screening and monitoring tests for antibacterials and other drugs serve to ensure compliance with the withdrawal periods. However, sampling and analytical errors in the measurement of milk residue concentrations are also possible.

4. Conclusion

The probability of a child consuming residues of veterinary medicinal products in milk in concentrations which would exceed the acceptable daily intake for residues of the particular drug would seem remote when based on the risk pathway and variability factors described. They would appear to be limited to those drugs where a high percentage of the ADI is allocated to milk and where the drug was likely to be present in milk in concentrations just below the MRL at the end of the withdrawal period.

Exposure assessments have shown that milk being processed at the dairy is very unlikely to contain residues of any concern for the consumer, because of the variability and uncertainty factors including dilution as described above. Surveillance results support these assessments as only few violations of the MRL are being observed in the national inspection programmes.

The safety factors are considered sufficient with regard to effects in children. The safety of 100 factor normally used in deriving the ADI would take account of susceptible sub-groups such as children.

Therefore, considering that the safety factors used for the establishment of MRLs ensure consumer protection and taking into account the other factors discussed above, it is concluded that the system in place for the establishment of MRLs for milk is adequate also for children.

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