European Medicines Agency
Veterinary Medicines and Inspections

EMEA/CVMP/SWP/367651/2005
9 December 2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

Comments on JECFA/Codex Alimentarius Statistical methods for the estimation of MRLs

Background:

Following its 62nd meeting (2004), the JECFA has published on their web site a statistically based approach to establish maximum residue limits (MRL) for veterinary drugs and a calculation program with examples (*http://www.fao.org/es/ESN/jecfa/statistical_en.stm*). JECFA has invited comments by 15 January 2006.

The statistical MRL calculation approach is based on linear regression analysis and statistical estimation of one-sided upper tolerance limits for the marker residue depletion in the individual target tissues. An iterative procedure is used to calculate for different time points on the depletion curve the intake of residues of concern in the food basket, based on tolerance limits for the marker residue and the corresponding ratios marker/total residues. The so calculated residue intake is compared with the ADI and the time point of depletion below the ADI is selected to determine the MRLs. Since these MRL concentrations reflect upper statistical tolerance limits, the method allows the simultaneous calculation of MRL and withdrawal times for a specific product under consideration ("*The time point selected to derive the MRLVDs is compatible with (established) practical withdrawal times of the veterinary drug*").

CVMP comment:

The CVMP would like to support the statistical methods for the estimation of MRLs.

Specific comments and considerations are provided:

The underlying statistical method is the same as that recommended by the CVMP for the calculation of withdrawal periods in tissues (tolerance limits according to the equation by Stange[1,2]). It is recommended to calculate the 95 % tolerance limit with 95 % confidence or, alternatively, a 95%/99% or 99%/99% tolerance limit to satisfy regulatory requirements outside the EU (e.g. FDA).

The idea is to derive MRLs at the time point when upper statistical tolerance limits for the marker residue in target tissues and the corresponding total residues in the food basket are compliant with the ADI and to calculate, by doing so, statistically based withdrawal periods and MRLs in one step. The approach is scientifically sound. If this approach is used, one needs to be aware, however, that the calculated withdrawal period is only valid for the specific product and dosing regimen used to generate the residue data and needs to be confirmed if other products are used. However, the calculated MRLs, once established, remain valid for other applications as well. This is different from the current practice as adopted by CVMP where an MRL is established based on the partitioning of mean residue levels between tissues at/around the time point when mean total residues deplete below

[1] Kurt Stange, Angewandte Statistik, Vol. II, pp. 141-143, Springer Verlag, Berlin, Heidelberg, New York, 1971
[2] EMEA CVMP (1995) *Note for Guidance: Approach Towards Harmonization of Withdrawal Periods*. EMEA/CVMP/036/95-Final.

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the ADI. The withdrawal periods are calculated in a different (statistical) procedure (see above) based on a residue depletion study using the *product.*

In practice, JECFA's calculations using upper tolerance limits for the marker residue may lead to MRLs that differ from those based on the current approach where mean marker residue concentrations are used. With the new proposed statistical approach the upper tolerance limit approach can have an impact on the relative distribution of the MRLs between tissues (liver:kidney:muscle:fat). In addition, there may be a more or less pronounced shift of the time point of depletion of residues below the ADI and this could affect the values for ratios marker/total residue used to estimate total residues[3]. It seems difficult at the moment to assess the direction or possible magnitude of such differences in practice (this is, of course, depending on the individual data set and data variability).

The JECFA approach is not considered to be inherently "safer" or "unsafer" than the currently used approaches. There is no additional margin of safety or an extra portion of the ADI reserved to allow for statistical variability. Both JECFA and CVMP usually use up the full ADI (as they see fit) and it is, therefore, mainly the relative concentration of the MRL between the target tissues where noticeable differences can be expected. In the past JECFA has already routinely used an iterative approach quite similar to what is now proposed. The approach was to set MRLs at an upper percentile of the marker residue distribution (e.g., mean + 3 SD instead of the upper tolerance limit).

A considerable limitation of the proposed approach could be that statistical requirements for a linear regression analysis have to be met in all (four) target tissues, which - according to practical experience - is only rarely the case. This may be the reason why JECFA has not applied the statistical approach very often in the past[4]. In addition, no statistically based approach allowing to calculate MRLs for milk or eggs is proposed. Simple linear regression analysis and calculation of upper tolerance limits according to the method used for tissues is not possible in these cases.

[3] May have a noticeable effect only if the ratios are not stable/changing rapidly with time

[4] Codex Alimentarius Commission; Report of the Fifteenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods, Washington D.C., USA, 26-29 October 2004 ("For several previous meetings JECFA has used a statistical approach for the estimation of MRLs, e.g. for eprinomectin and dicyclanil")