EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The MRL evaluation of pharmacologically active substances used in veterinary medicinal products

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An agency of the European Union

Aspects to cover

- Regulatory aspects
- Safety evaluation
- Residues evaluation
- Biocides for use in animal husbandry

Regulatory aspects

Regulation EC (No) 470/2009 laying down Community procedures for the establishment of residue limits for pharmacologically active substances in foodstuffs of animal origin, relates to:

- residues of pharmacologically active substances used in veterinary medicines intended for food producing animals
- residues of pharmacologically active substances used in biocidal products used in animal husbandry

Regulatory aspects

Scientific evaluation performed by EMA's Committee for Medicinal Products for Veterinary Use (CVMP)

=> recommendations to European Commission

Consultation with Member States. If agreement,

=> Publication in EU Official Journal and inclusion in the annex to Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding MRLs in foodstuffs of animal origin

Regulatory aspects

Regulation 470/2009 specifies a 210 day evaluation period

- Letter of intent 6 to 3 months before application – assign rapporteurs
- 15 working day validation period – is the file complete?
- 210 day evaluation period:
- 120 days for initial evaluation by rapporteurs
- Clock stop for response
- 90 day period for evaluation of responses
- must be managed so that key steps (eg, list of questions, final opinion) coincide with CVMP meeting dates => fixed submission dates

Regulatory aspects

Possible outcomes according to Regulation 470/2009:

- Numerical MRLs
- Provisional MRLs
- No MRL required

Table 1 of annex to Regulation 37/2010

- Prohibition of use of the substance

Table 2 of annex to Regulation 37/2010

Note that Regulation 470/2009 does not foresee default MRLs

More information on procedural aspects on EMA website, at http://www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2010/02/WC500074589.pdf

Regulatory aspects

Consideration of exposure from other sources:

Art 6 of Regulation 470/2009:

"The scientific risk assessment shall concern the following…

…residues that occur in food of plant origin or that come from the environment"

For dual VMP/pesticide use substances rough guidance has been to reserve 45% for veterinary use.

Regulatory aspects

Extrapolation of MRLs:

Art 5 of Regulation 470/2009:

"…the Agency, while ensuring a high level of protection of human health, shall, when carrying out scientific risk assessments and when drawing up risk management recommendations, consider using maximum residue limits established for a pharmacologically active substance in a particular foodstuff for another foodstuff derived from the same species, or maximum residue limits established for a pharmacologically active substance in one or more species for other species."

Safety evaluation

Focused on deriving an ADI based on consideration of toxicological, pharmacological and microbiological effects

Toxicological ADI based on:

- Repeat dose testing: 90 day oral studies in 1 rodent and 1 non-rodent species (VICH GL 31)
- Chronic toxicity testing in at least 1 species, typically rat (VICH GL 37)
- Reproductive toxicity testing: 2 generation study in at least 1 species (VICH GL 22)
- Developmental toxicity testing: Test rat – if results negative or equivocal, then test rabbit (VICH GL 32)

Safety evaluation

- Genotoxicity testing:
  - gene mutation in bacteria (Ames test)
  - cytogenetic test for chromosomal damage (in vitro metaphase chromosome aberration or in vitro micronucleus) or in vitro mouse lymphoma tk gene mutation test
  - in vivo test for chromosomal effects using rodent haematopoietic cells (VICH GL 23)
- Carcinogenicity testing (if positive genotox data / structure activity relationship / relevant findings in repeat dose studies): normally studies in both rat and mouse (VICH GL 28)
- Other (immungenicity, neurotoxicity – if a particular concern is identified)

Safety evaluation

The pharmacological ADI:

- The intended pharmacological effect in the target animal is an adverse effect in the consumer exposed to residues
- A pharmacological ADI needs to be established when pharmacological effects resulting from residues can be expected at doses in same range or lower than toxicological effects.
- Studies to be performed will depend on the specific pharmacological action of the substance
- In some cases these may already be covered in toxicity studies
- The lowest pharmacological NOAEL is used as the basis for the pharmacological ADI

(CVMP GL on approach to establish a pharmacological ADI)

Safety evaluation

The microbiological ADI:

- Residues with antimicrobial activity may have adverse effects on the bacterial flora in the human gut – the overall ADI should take account of these

2 endpoints considered:

- Disruption of colonisation barrier (which may lead to colonisation by potentially pathogenic bacteria)
- Increase of population(s) of resistant bacteria (ie increase in populations insensitive to the drug, which may be due to acquisition of resistance by previously sensitive organisms or to a relative icrease in proportion of organisms that are already less sensitive)

In most cases the mADI is derived form MIC data against human intestinal bacteria
(VICH GL 36 on general approach to establish a microbiological ADI)

Safety evaluation

Overall ADI is lowest of the toxicological, pharmacological and microbiological ADIs

Note: CVMP approach based on ADI – no ARfD

Assumption is that exposure is chronic (do not use a 'short term' food basket)

However, CVMP ADI covers certain acute effects:

- Pharmacological effects
- Microbiological effects

Residues evaluation

Data required from:

- Comparative metabolism studies
- Total residue depletion studies in target species
- Marker residue depletion studies in target species
- Analytical methods suitable for residue control

Calculation of residue intake based on residue levels at different time points after administration allows derivation of the MRLs

Guidance on all aspects available in Volume 8 of the Rules governing medicinal products in the European Union

Residues evaluation

Comparative metabolism studies

- Demonstrate that laboratory species from which ADI is derived were exposed to same residues to which consumers will be exposed as a result of consuming animal produce

Total residue depletion studies in target species

- Information on ADME in target tissues
- Depletion of total residues from target species
- Identification of marker residue:
  - component of the total residues (or a chemical derivative) – often the parent
  - Known relationship with total residues (marker to total residues)
  - Appropriate for residue monitoring

Residues evaluation

Marker residue depletion studies in target species

- Provides evaluation of residue levels at different time points
- Compare intake at different time points to establish MRLs

Analytical method suitable for residue control

- Setting of MRLs requires availability of an analytical method for all relevant tissues (no MRL without analytical method)
- Provides basis for official residue monitoring and surveillance method

Residues evaluation

Analytical method description:

- Provided in an internationally recognised standard layout

Details to include:

- purpose and scope;
- reagents; equipment;
- collection of samples; storage of samples;
- preparation of the validation sample(s);
- preparation/clean-up ;
- analytical methodology;
- calculation of results (calibration parameters etc);
- quality control measures

Residues evaluation

Analytical method validation:

- Specificity
- Accuracy
- Precision
- Limit of detection
- Limit of quanitification
- Practicability/Applicability
- Susceptibility to interference
- Stability of analyte

Residues evaluation

The intake calculation

Uses the Theoretical Maximum Daily Intake (TMDI):

Mammals	Poultry	Fish	Bees
Meat: 300g muscle 100g liver 50g kidney 50g fat 1.5kg milk	Meat: 300g muscle 100g liver 10g kidney 90g fat 100g eggs	Meat: 300g muscle + skin in natural proportions	20g honey

Residues evaluation

The intake calculation:

Tissue intake = marker concentration x $\frac{\text{food consumption factor}}{\text{Marker:total}}$

TMDI = combined intake from all tissues and commodities

Point of departure for MRL = residue levels at time point at which TMDI falls below the ADI

Final MRL will take account of proportion of ADI already used taken up by other uses including (VMP uses in other species, pesticide use, biocide use) and need to maintain an unused portion of ADI for future uses (eg, could substance be uses in dairy cattle?)

Residues evaluation

Extrapolation

Species for which MRLs have been set	Extrapolation to
Major ruminant	All ruminants
Major ruminant milk	All ruminants milk
Major monogastric mammal	All monogastric mammals
Chicken and eggs	Poultry and poultry eggs
Salmonidae	All fin fish
Either major ruminant or monogastric mammal	Horses

Marker residue should be shown to exist in a minor species and analytical method for major species shown to be applicable

Biocides for use in animal husbandry

CVMP/DRAWG group developed a draft guideline on risk characterisation and assessment of Maximum Residue Limits (MRL) for biocides – published for consultation at end of 2011

Proposes step-wise approach:

- Need for MRL evaluation determined using a threshold approach (if external exposure > 4µg/kg/day => MRL evaluation)
- MRL evaluation starts with a Worst Case Consumer Exposure estimate and comparison to the ADI
- WCCE can be refined (eg based on absorption considerations)
- If (refined) WCCE clearly < ADI without implementation of exposure reduction measures => recommendation for 'No MRL required' status or numerical MRLs for control purposes

Biocides for use in animal husbandry

- If exposure reduction measures needed to bring exposure below ADI => MRLs needed
- MRLs set so that compliance with the MRLs would indicate compliance with the exposure reduction measures
- Possibility of deriving MRLs without formal residue data not ruled out (would require use of scientifically justifiable assumptions on residue distribution, eg based on existing data in other species)
- In many cases residue data would be needed

Biocides for use in animal husbandry

- Residue data requirements based on those that exist for VMP active substances, although possibility to deviate from these based on scientific justification
- Test substance should be representative of substance to which animals will be exposed. Default route of administration is oral (except for direct administration products)

At product evaluation:

CA would need to satisfy itself that the proposed exposure reduction measures ensure compliance with the MRLs

Biocides for use in animal husbandry

Consultation on Guideline

- Few comments received
- Main concern raised was that trigger for MRL evaluation considered too low with result that almost all biocidal substances for use in animal husbandry would require MRL evaluations

Ongoing activity:

- Review draft guideline and consider how above concern might be addressed
- Change triggering event so that it is based on the (refined) WCCE rather than on external exposure of animal??