Risk Assessment Veterinary Medicinal Products
Göttingen, February 26, 2018
Hans van Hattum, DVM
Veterinary Medicinal Product
VMP
Marketing Authorisation
Dossier for application for Marketing Authorisation as VMP

• Part 1: Summary of the Dossier
• Part 2: Pharmaceutical Information
• Part 3: Safety + Residues
• Part 4: Efficacy
Safety

- Animal Safety
- Human Safety
- Environmental Safety
Animal Safety

- Toxicity: active ingredient: rat, rabbit, etc
- Tolerance: final formulation: target species
Human Safety

• User Safety
• Consumer Safety
User Safety

Definition of User:
Any person that may come in contact with the VMP:
• before
• during
• after
its application
Human Safety

• User Safety
Human Safety

• User Safety
Human Safety

• User Safety
User Safety

User Risk Assessment:

• Hazard identification and characterisation
• Exposure
• Risk
User Safety

User Risk Assessment:
• Hazard identification and characterisation
  o Toxicity active(s)

NO(A)EL
User Safety

User Risk Assessment:

• Hazard identification and characterisation
• Exposure
• Risk
User Safety

User Risk Assessment:

- Exposure
  - Presentations, use, physico-chemical properties
  - Tasks and situations that lead to exposure
  - Exposure scenarios
User Safety

User Risk Assessment:
• Exposure: Tasks and situations
  o **Before** application:
    ➢ Storage
    ➢ Opening Package, taking out tablet
    ➢ Mixing
    ➢ Diluting
    ➢ Filling syringe
User Safety

User Risk Assessment:
• Exposure: Tasks and situations
  o **During** application:
    ➢ Administration
    ➢ Holding/restraining animal for treatment
User Safety

User Risk Assessment:

• Exposure: Tasks and situations
  
  o **After** application:
    ➢ Cleaning equipment
    ➢ Disposal packaging
    ➢ Disposal surplus product
    ➢ Handling treated animals
    ➢ Stroking the coat of treated animals
User Safety

User Risk Assessment:

- Exposure
  - Presentations, use, physico-chemical properties
  - Tasks and situations that lead to exposure
  - Exposure scenarios
User Safety

User Risk Assessment:
• Hazard identification and characterisation
• Exposure
• Risk
User Safety

User Risk Assessment:
  • Risk
    o Risk characterisation
    o Risk management
    o Risk communication
User Safety

User Risk Assessment: **Topical administration**

**Product:**
Spot-on solution, pipette; Cat

**Contact with the product**

**Exposure, worst-case:**
Pre-application: accidental oral, child (12.5 kg)
User Safety

User Risk Assessment: **Topical administration**

**Product:**
Spot-on solution, pipette; Cat

**Contact with the product**

**Exposure, worst-case:**
Direct oral exposure: 10% of contents
In-direct oral exposure: 10% x 10% = 1% of contents

\[
\text{Exposure} = \frac{\text{Contents} \times \text{Fraction}}{\text{Body weight}}
\]
User Safety

User Risk Assessment: **Topical administration**

**Product:**
Spot-on solution, pipette; Cat

**Contact with the treated animal**

**Acute Dermal Exposure**
User Safety

User Risk Assessment: Acute Dermal Exposure

DE = Dermal Exposure (mg/kg bw/day)
TR = Transferable Residue: concentration of the active per surface area of the cat that may transfer to the child (mg/cm$^2$)
SA$_{contact}$ = surface area child in contact with the animal (= 1790 cm$^2$)

$$DE = \frac{TR \times SA_{CONTACT}}{BW}$$
User Safety

User Risk Assessment: Acute Dermal Exposure

\[ TR = \text{Transferable Residue (mg/cm}^2\text{)} \]

\[ AR = \text{Application Rate: amount of active applied to the animal (mg)} \]

\[ F_{AR} = \text{Fraction of the Application Rate (} = 15\%) \]

\[ SA_{ANIMAL} = \text{Surface Area of the animal (cat 2500 cm}^2\text{)} \]

\[ TR = \frac{AR \times F_{AR}}{SA_{ANIMAL}} \]
Human Safety

• Consumer Safety
Consumer Safety

Residues → Withdrawal Period
Consumer Safety

Withdrawal period:

Period after last administration during which consumption of meat, eggs and milk is not safe, because of residues of the veterinary medicinal product.
Consumer Safety

Basis for the establishment of the withdrawal period:

**MRL**

Maximum Residue Limit
Consumer Safety

MRL is established by EMA on the basis of MRL-dossier submitted by veterinary pharmaceutical company.

New active? → MRL dossier
Consumer Safety

MRL is established by EMA on the basis of MRL-dossier submitted by veterinary pharmaceutical company.

New active? → MRL dossier

No MRL for the active? → No Marketing Authorisation
Consumer Safety

MRL should be established:
  • For each edible tissue
  • For each target species
## Consumer Safety

### Edible Tissues

<table>
<thead>
<tr>
<th>Mammals</th>
<th>Poultry</th>
<th>Fish</th>
<th>Bees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>Muscle</td>
<td>Muscle+Skin</td>
<td>Honey</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>Skin+Fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin+Fat (pig)</td>
<td>Skin+Fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>Eggs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Consumer Safety

Basis to determine MRL:

• Acceptable Daily Intake (ADI)
• Body Weight Consumer
• Consumption Figures
• Marker Residues
• Distribution in Edible Tissues
Consumer Safety

Basis to determine MRL:

- Acceptable Daily Intake (ADI)
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Consumer Safety

MRL Dossier

Toxicity studies → NO(A)EL → ADI

Acceptable daily intake (ADI): the estimate of the residue (\(\mu g/kg\) or \(mg/kg\) of bodyweight), that can be ingested daily over a lifetime without any appreciable health risk.
Consumer Safety

MRL Dossier: Toxicity studies
• Repeated dose 90-day oral studies: rat, dog
• Repeated dose (chronic) toxicity studies: rat
• Two-generation reproduction study: rat
• Development toxicity: rat, rabbit
• Battery of mutagenicity

Additional studies:
• Carcinogenicity studies
• Other tests: Immunotoxicity, neurotoxicity, etc

In compliance with GLP (Good Laboratory Practice)
Consumer Safety

MRL Dossier: Toxicity studies → NO(A)EL

NO(A)EL  Animal toxicity data
ADI  Human beings

Determination ADI:

\[ ADI = \frac{NO(A)EL}{UF} \]

UF = Uncertainty (Safety) Factor
Consumer Safety
MRL Dossier, Residue File

ADI → MRL
Consumer Safety
MRL Dossier, Residue File

Maximum acceptable residue daily intake to be ingested by the consumer:

Body weight 60 kg

Maximum intake: $ADI \times 60$
Consumer Safety
MRL Dossier, Residue File

ADI \times 60 \rightarrow \text{MRL}
Consumer Safety
MRL Dossier, Residue File

ADI x 60 → MRL
Consumer Safety
MRL Dossier, Residue File

ADI x 60  →  MRL
Consumer Safety
MRL Dossier

ADI x MRL
Consumer Safety
MRL

A
## Consumer Safety

### MRL Dossier

#### Food basket

<table>
<thead>
<tr>
<th></th>
<th>Mammals (kg)</th>
<th>Poultry (kg)</th>
<th>Fish (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>0.300</td>
<td>Muscle</td>
<td>0.300</td>
</tr>
<tr>
<td>(Skin+) Fat</td>
<td>0.050</td>
<td>Skin+ Fat</td>
<td>0.090</td>
</tr>
<tr>
<td>Liver</td>
<td>0.100</td>
<td>Liver</td>
<td>0.100</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.050</td>
<td>Kidney</td>
<td>0.010</td>
</tr>
</tbody>
</table>

#### PLUS

<table>
<thead>
<tr>
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<th>(kg)</th>
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<tbody>
<tr>
<td>Milk</td>
<td>1.500</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.100</td>
</tr>
<tr>
<td>Honey</td>
<td>0.020</td>
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Consumer Safety

MRL Dossier

Basis to determine MRL:

• Acceptable Daily Intake (ADI)
• Body Weight Consumer
• Consumption Figures
• Distribution in Edible Tissues
Consumer Safety

MRL Dossier

Distribution in edible tissues
MRLs should be based on the tissue residues distribution pattern of the active substance
Consumer Safety

MRL Dossier

Distribution in edible tissues
MRLs should be based on the tissue residues distribution pattern of the active substance

Determination of distribution:

Tissue residue study
Consumer Safety
Tissue Residue Study

For example:
Target Species: Cattle
ADI: 1.50 μg/kg

Body Weight 60 kg \(\rightarrow\) Max Daily Intake: 90 μg
Consumer Safety
Tissue Residue Study

Design
24 animals: Cattle
  6 groups, 4 animals each
Administration active
Slaughtering: 3, 6, 9, 12, 15, 18 days post dosing
Analyses: concentration in liver, kidney, fat, muscle
## Consumer Safety

### Tissue Residue Study

<table>
<thead>
<tr>
<th>Days post dosing</th>
<th>Liver (µg/kg)</th>
<th>Kidney (µg/kg)</th>
<th>Fat (µg/kg)</th>
<th>Muscle (µg/kg)</th>
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<tbody>
<tr>
<td>3</td>
<td>799</td>
<td>1022</td>
<td>213</td>
<td>75.1</td>
</tr>
<tr>
<td>6</td>
<td>567</td>
<td>665</td>
<td>150</td>
<td>57.3</td>
</tr>
<tr>
<td>9</td>
<td>335</td>
<td>307</td>
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</tr>
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<tr>
<td>Food basket</td>
<td>0.100</td>
<td>0.050</td>
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<td>0.300 kg</td>
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**Distribution**

- 8
- 8
- 2
- 1

**Max Daily Intake**

<table>
<thead>
<tr>
<th>MRL possible</th>
<th>240</th>
<th>240</th>
<th>60</th>
<th>30</th>
<th>48.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRL possible</td>
<td>320</td>
<td>320</td>
<td>80</td>
<td>40</td>
<td>64.0</td>
</tr>
</tbody>
</table>
Consumer Safety

MRL $\rightarrow$ Withdrawal period
Consumer Safety

Withdrawal period:
Withdrawal period depends on the individual formulation

Marketing Authorisation Dossier!
Consumer Safety

Withdrawal period:

Tissue Residue Study
Consumer Safety

Withdrawal period:

Tissue Residue Study
Consumer Safety
Tissue Residue Study

• Final Formulation!!!
• Target Species
• Dosing according to Marketing Authorisation
• Good Laboratory Practice
Consumer Safety
Tissue Residue Study

Design, for example:
• Cattle
• 4 groups, 6 animals each
• Slaughtering groups at 7, 14, 21, 28 days post dosing
• Analyses liver, kidney, muscle, fat
Consumer Safety

![Graph showing Marker Residue/Cattle in Liver over time](image)

- **Marker Residue/Cattle**
- **Time (days)**
- **b) 95% tol. limit with 95% confidence interval**
- **c) Linear regression line**
- **MRL**
# Consumer Safety

**Withdrawal Periods**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>28 days</td>
</tr>
<tr>
<td>Kidney</td>
<td>10 days</td>
</tr>
<tr>
<td>Muscle</td>
<td>14 days</td>
</tr>
<tr>
<td>Fat</td>
<td>10 days</td>
</tr>
</tbody>
</table>

**Overall Withdrawal Period:** 28 days
Safety

Product on the market:

Pharmacovigilance