Human and veterinary pharmaceuticals regulation
Towards EU accession: Serbia's regulatory challenges, expectations and opportunities
29-30 November 2010
Hotel Holiday Inn, Belexpo Convention Centre, Belgrade, Serbia

Republika Srbija
Ministarstvo zdravlja
Ministarstvo poljoprivrede, šumarstva i vodoprivrede,
Uprava za veterinu

Republic of Serbia
Ministry of Health
Ministry of Agriculture, Forestry and Water Management,
Veterinary Directorate

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Agencija za lekove i medicinska sredstva Srbije
Medicines and Medical Devices Agency of Serbia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

User safety and environmental safety

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User safety

Airborne contact dermatitis due to ethacridine lactate in a veterinary surgeon

An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers

Needlestick injuries among female veterinarians: frequency, syringe contents and side-effects

Accidental self inoculation with oil based veterinary vaccines

Occupational allergic contact dermatitis due to airborne spiramycin

Unintentional Human Exposure to Tilmicosin

Accidental Veterinary Antibiotic Injection Into a Farm Worker

Operator Safety During Injection Vaccination of Fish

Severe Intoxication with the Veterinary Tranquilizer Xylazine in Humans

Anesthetic Gas Exposure in Veterinary Clinics

ANESTHESIA HAZARDS TO ANIMAL WORKERS

Health Symptoms and Occupational Exposure to Flea Control Products among California Pet Handlers*

Who is the user?

Any person that may come into contact with the veterinary medicinal product (VMP) or components of the product before its application to the animal (for example, during storage or preparation), during its application, and after its application (for example, through contact with the treated animals)

Who is the user?

The veterinarian?

The children?

The owner?

The contract worker?

The farmer?

The groom?

User safety assessment

Guideline on user safety for pharmaceutical veterinary medicinal products

EMA/CVMP/543/03-Rev.1

Date for coming into effect: 1 October 2010

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500077971.pdf

Steps of the risk analysis

1. Hazard identification and characterisation
2. Exposure assessment
3. Risk assessment
4. Risk management
5. Risk communication

Risk Analysis (according to Scott Adams)

Step 1: Hazard identification and characterisation

- Make use of the toxicological data in the safety file
- Evaluate local toxicity (formulation)
- Evaluate systemic toxicity (active ingredients)

Step 2: Exposure assessment

- Identify the tasks and situation that lead to human exposure
- Describe the exposure scenario's
  - Type of user
  - Route(s) of human exposure
  - Probability of human exposure
  - Rate, extent, duration, interval, and frequency of exposure

Step 3: Risk assessment

Compare the hazards with the exposure

Is there a risk for *unprotected* users at the anticipated exposure scenario's?

Step 4: Risk management

- restriction of the category of user, e.g. to use by veterinarians only;
- excluding groups at risk, e.g. sensitised people, pregnant women;
- restriction of application methods, e.g. pour-on instead of spraying;
- restriction of the field of use, e.g. outdoor use only;
- modification of packaging, e.g. reduced pack size;
- modification of labelling;
- modification of measures for the protection of users, e.g. general controls like ventilation or personal protective equipment like protective gloves.

Step 5: Risk communication

SPC, label, package insert

Elements of a user safety warning in the product documentation

What is the risk

A. What is the risk
B. What exposure must be avoided/reduced
C. How to avoid/reduce exposure
D. What to do in case of (accidental) exposure

Example:

A. Can cause eye irritation
B. Avoid contact with the eyes
C. Wear eye protection
D. In case of exposure immediately rinse with plenty of water

Benefit / Risk Balance

Only in those cases where the risks for the user cannot be sufficiently prevented by risk management measures and warnings, and these risks are not outweighed by the benefits of the product, the benefit/risk balance may become negative.

References

- Directive 2001/82/EC of the European Parliament and of the Council as amended by Directive 2004/28/EC and Directive 2009/9/EC

  (eur-lex.europa.eu)

- Rules Governing Medicinal Products in the EU: Notice to Applicants, Volume 6B "Presentation and content of the Dossier“

  (http://ec.europa.eu/health/files/eudralex/vol-6/b/vol6b_04_2004_final_en.pdf)

- Guideline on user safety for pharmaceutical veterinary medicinal products

  (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500077971.pdf)

Environmental safety

Antibiotics Threaten Wildlife: Circulating Quinolone Residues and Disease in Avian Scavengers

Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent

Environmental risk assessment (ERA)

The ERA is performed in two phases:

PHASE I – exposure-based decision tree to identify the products that need a full ERA

PHASE II - full ERA: refined exposure, fate, effects. Risk management if necessary.

Phase I works as a filter

Not all VMPs get a full ERA.

The Phase-I filters out the products with low scope for environmental contamination, such as:

- Companion animals
- Products for individual treatment

A full ERA (Phase-II) is mainly limited to:

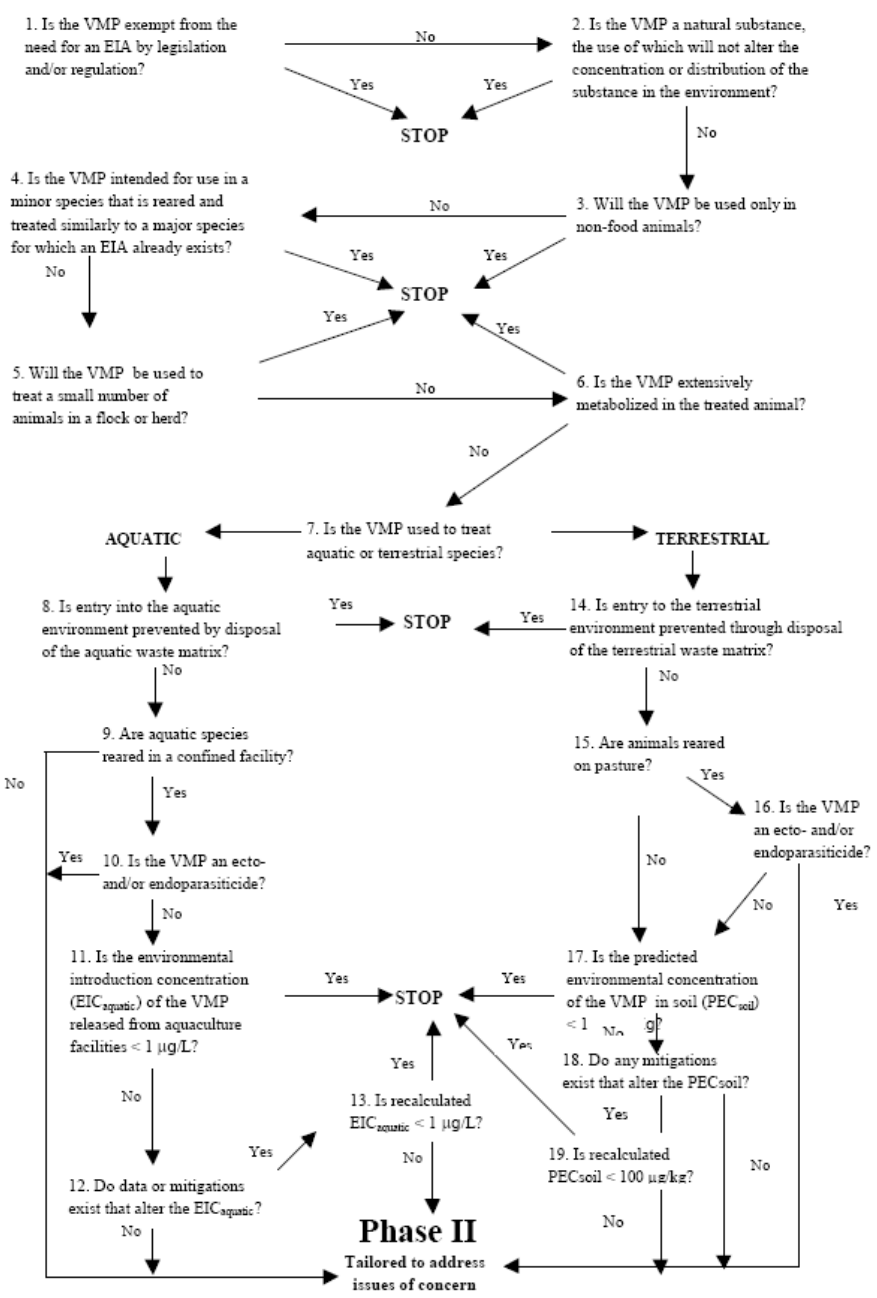
- products for group treatment of food producing animals
- Products for treatment of endo-/ectoparasites in food producing animals reared on pasture

Phase I

Goal of the Decision tree:

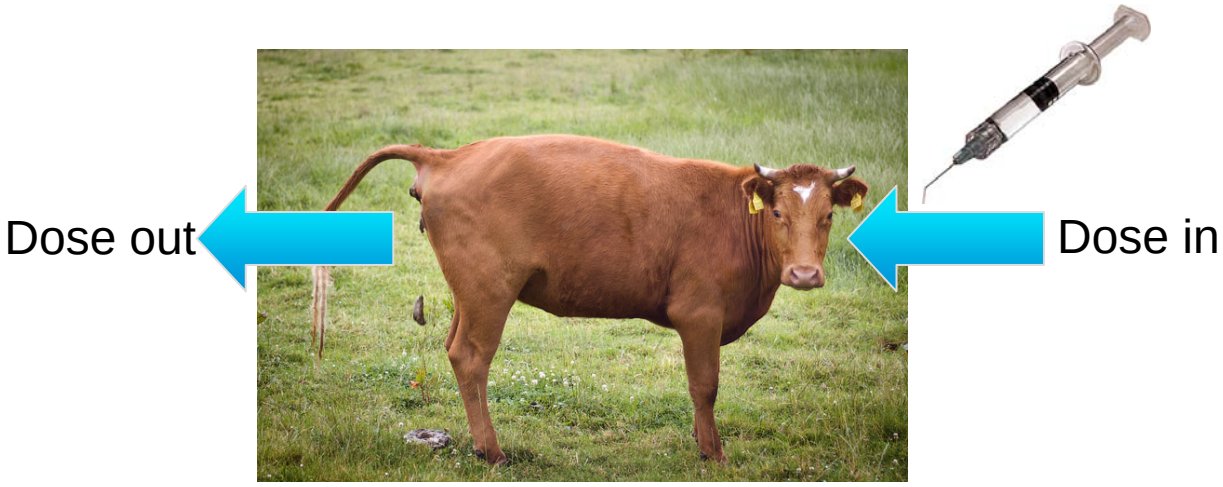
- High environmental exposure: go to Phase II
- Low environmental exposure: no further assessment

Figure 1. Phase I Decision Tree



Phase I

Exposure assessment based on worst-case:



dose in = dose out

Phase II

- Refinement of exposure
  - Metabolism in animals
  - Excretion profiles
- Fate in the environment
  - Degradation in (stored) manure
  - Degradation in soil
  - Leaching to groundwater
- Effects in the environment
  - Water compartment (fish, algae, invertebrate)
  - Soil compartment (plants, earthworms, micro-organisms)
  - Dung organisms (dung beetle, dung fly)

Outcome Phase II

Risk Quotient approach

$$\text{Risk Quotient (RQ)} = \frac{\text{Predicted Environmental Concentration (PEC)}}{\text{Predicted No Effect Concentration (PNEC)}}$$

If RQ < 1, no further testing is required

If RQ > 1, then:

- Further testing ("Tier B") and PEC-refinement
- Propose risk management
- Ultimately, consider risk in benefit/risk balance

References

VICH Guideline 6: ERA Phase I

(www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004394.pdf)

VICH Guideline 38: ERA Phase II

(www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004393.pdf)

CVMP ERA in support of VICH GL 6 and 38, EMEA/CVMP/ERA/418282/2005-Rev.1

(www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004386.pdf)

Notice to Applicants, Volume 6C: Guidance on the Assessment of environmental risks of veterinary medicinal products

(ec.europa.eu/health/files/eudralex/vol-6/ne_en_doc/2009-03-17_era-cvmp_nta_en.pdf)