Human and veterinary pharmaceuticals regulation

Towards EU accession: Serbia's regulatory challenges, expectations and opportunities

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EUROPEAN MEDICINES AGENCY
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# Maximum Residue Limits (MRLs) and Consumer safety

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# Overview

- Consumer safety and MRLs
- Procedure for the establishment of MRLs in the EU
- Data requirements and assessment
- Implementation and residue control
- Information on MRLs made publicly available by the Agency

# Consumer safety

**Main principles:**

- Foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues which might constitute a health hazard to the consumer

Through:

- Establishment of maximum residue limits (MRLs) as pre-condition for marketing authorisation for veterinary medicinal product for food-producing animals
- Establishment of withdrawal period within marketing authorisation procedure
- Residue surveillance

# Legal basis for the establishment of maximum residue limits (MRLs)

- Regulation (EC) No 470/2009 (repealing Regulation (EEC) No 2377/90) http://ec.europa.eu/health/files/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf

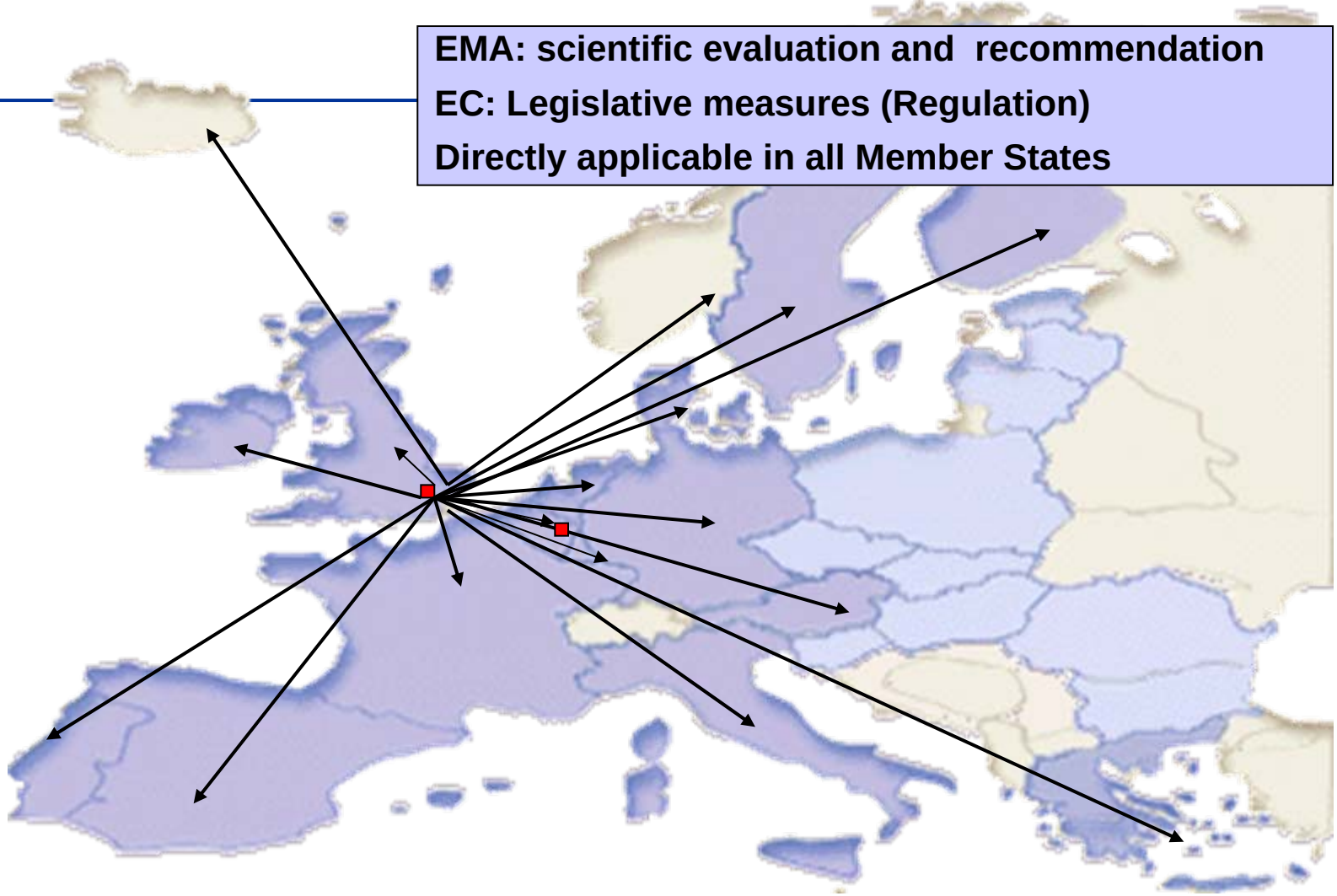
- Defines the procedure for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin

# Establishment of MRLs in the EU

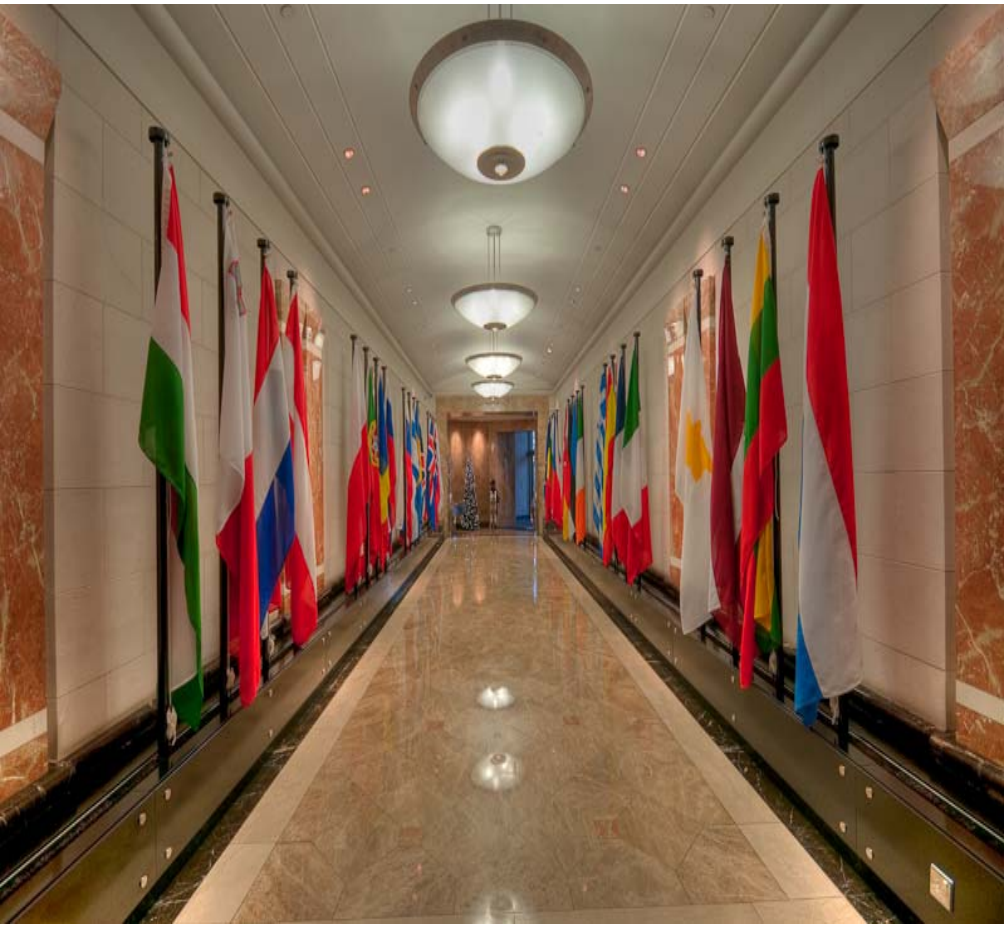
**EMA: scientific evaluation and recommendation**

**EC: Legislative measures (Regulation)**

**Directly applicable in all Member States**



# European Medicines Agency role



- To provide to the European Commission with a scientific opinion with regard to the establishment of MRLs
- The opinion follows the evaluation of the safety of residues carried out by the Committee for Medicinal Products for Veterinary Use (CVMP) upon receipt of a valid application

# Requests for establishment of MRLs

**Requests can be submitted to the EMA by**:

- A company with the aim to establish a MRL for a new substance, a new species or a new food commodity

- The European Commission or a Member State for:
  - A substance included in a product authorised in a non-EU country
  - A substance included in a veterinary medicine used in a different animal species

# Data requirements for establishment of maximum residue limits

- **Implementation rules** to be established by European Commission further to Article 13 of Regulation 470/2009 – in the meantime Annex V of Regulation 2377/90 applies
- **Volume 8** of the Notice to Applicants and Guideline: establishment of maximum residue limits – currently under review to take into account the new MRL Regulation
- **CVMP Guidelines** on how to carry out the studies on pre-clinical safety and residue depletion

# Principles of MRL evaluation


NOEL (NO OBSERVED EFFECT LEVEL (mg/kg bw/day))

**Uncertainty factor**

ADI (Acceptable Daily Intake (mg/person))

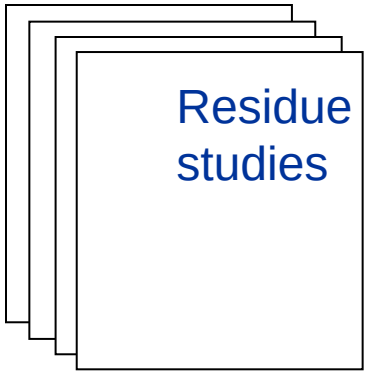
- Toxicological ADI
- Microbiological ADI
- Pharmacological ADI

Taking into account the food basket:

300 g muscle
50 g kidney, fat
100 g eggs
100 g liver
1.5 l milk
20 g honey

MRL (Maximum Residue Limit (µg/kg)

Analytical method for residue control (if applicable)



# CVMP evaluation (1/4)

- Rapporteurs are appointed following receipt of a letter of intent for submission of an application
- EMA checks conformity of the dossier within 10 days of receipt according to legal requirements and validates the dossier
- Rapporteurs assess the data and produce an assessment report
- Other CVMP members comment on the assessment report
- Peer reviewers scrutinise the scientific content of the report

# CVMP evaluation (2/4)

- Consideration of possibility for extrapolation of MRLs during the assessment
- Consultation of Community Reference Laboratories (CRLs) with regard to the analytical method proposed by the applicant for monitoring purposes

# CVMP evaluation (3/4)

## Analytical methods

- With the application for the establishment of MRLs the company must submit an analytical method for monitoring of residues.

- The suitability of the analytical method is one of the evaluation criteria.

# CVMP evaluation (4/4)

## Collaboration with the European Food Safety Authority (EFSA)

- The CVMP opinion has to take into account any relevant scientific findings of the European Food Safety Authority (EFSA) (dual use substances: pesticides, feed additives, food additives)

# Possible outcome of evaluation (1/2)

## Positive

- MRLs established
- Provisional MRLs established with a deadline to resolve outstanding issues
- MRLs not required for protection of public health

# Possible outcome of evaluation (2/2)

## Negative

- No MRLs established as no safe limit can be identified
- No MRLs established as no final conclusion concerning the effect on human health can be drawn

# Maximum residue limits (MRLs) established in the EU

## Regulation (EC) No 37/2010

Alphabetical list of pharmacologically active substances, including marker residue, target species, MRL values/status, target tissues, other provisions and therapeutic classification

http://ec.europa.eu/health/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf

- Table I : Allowed substances
- Table II: Forbidden substances

# MRLs in the Official Journal



*ANNEX*

**Pharmacologically active substances and their classification regarding maximum residue limits (MRL)**

*Table 1*

**Allowed substances**

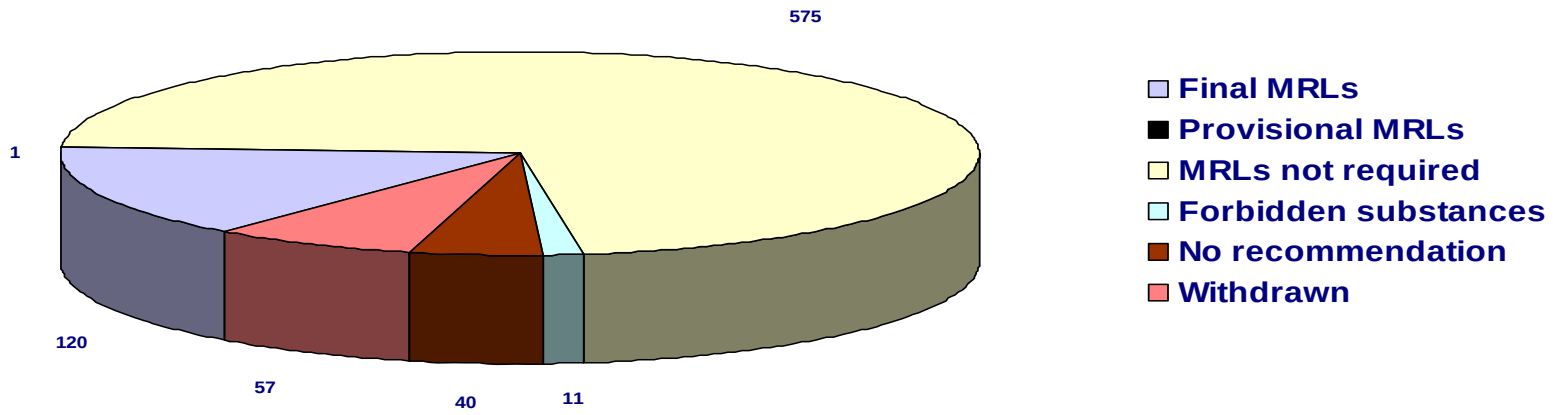
| Pharmacologically active Substance | Marker residue | Animal Species | MRL | Target Tissues | Other Provisions (*according to Article 14(7) of Regulation (EC) No 470/2009*) | Therapeutic Classification |
|---|---|---|---|---|---|---|
| Abamectin | Avermectin B1a | Bovine | 10 µg/kg<br>20 µg/kg | Fat<br>Liver | NO ENTRY | Antiparasitic agents/Agents acting against endo- and ectoparasites |
| | | Ovine | 20 µg/kg<br>50 µg/kg<br>25 µg/kg<br>20 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | Not for use in animals from which milk is produced for human consumption. | |
| *Absinthium* extract | NOT APPLICABLE | All food producing species | No MRL required | NOT APPLICABLE | NO ENTRY | NO ENTRY |
| Acetyl cysteine | NOT APPLICABLE | All food producing species | No MRL required | NOT APPLICABLE | NO ENTRY | NO ENTRY |
| Acetylmethionine | NOT APPLICABLE | All food producing species | No MRL required | NOT APPLICABLE | NO ENTRY | NO ENTRY |

# Forbidden substances

- *Aristolochia* spp and preparations thereof
- Chloramphenicol
- Chloroform
- Chlorpromazine
- Colchicine
- Dapsone
- Dimetridazole
- Nitrofurans (including furazolidone)
- Ronidazole

# Overview of MRLs established in the EU

Over 800 substances assessed by CVMP



# Implementation and residue control

- Following publication of MRLs in the Official Journal of the European Communities (OJ): the analytical method is submitted to the Community and national Reference Laboratories (if relevant)
- The responsibility for monitoring residues of veterinary medicinal products in foodstuffs of animal origin lies with the competent authorities of the EU Member States

# Consumer safety / marketing authorisations

In order to obtain a marketing authorisation, all pharmacologically active substances, included in the product intended for food-producing animals must undergo an evaluation of the safety of residues

**No marketing authorisation if no MRL established**

# Other aspects of the new MRL Regulation

- Establishment of MRLs for biocides used in animal husbandry
- Codex MRLs retained as EU MRLs as far as agreed by EU at Codex Commission level
- Establishing Reference Points for Action to ensure functioning of control when no MRL is established

# Information on MRLs

Information is available on the Agency's website

http://www.ema.europa.eu/

- Summary opinions
- Opinions
- European Public MRL Assessment Reports (EPMARs)
- Guidelines

Queries on MRLs: mrl@ema.europa.eu

# SUMMARY

- MRLs are established at Union level only and are directly applicable in all Member States
- Agency: scientific evaluation ⇨ recommendation to the European Commission
- European Commission: Legislative measures
- Member States: Monitoring (EC coordination)
- No MRLs: no marketing authorisation for medicines intended for food producing species


# Thank you for your attention