EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Consumer safety and Maximum residue limits (MRLs)

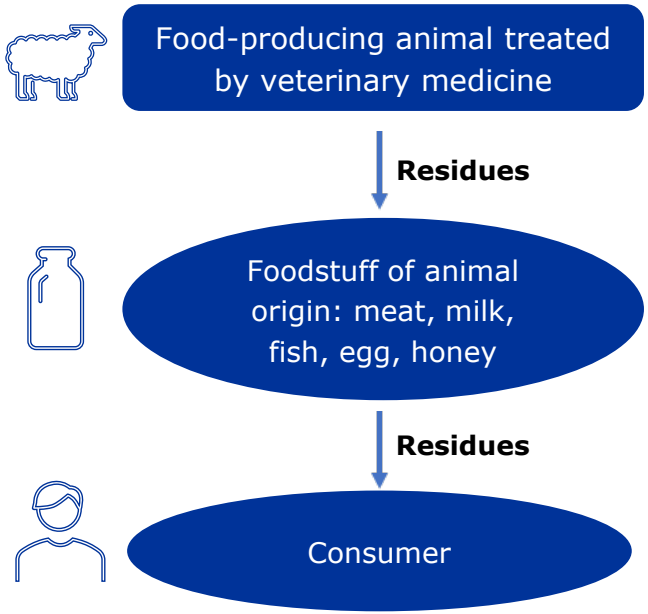
EMA Veterinary Awareness Day

Presented by Sebastien Girault on 12 September 2023
Scientific Administrator

Overview

- Notions of residues and consumer safety
- Consumer safety in MRL (Maximum Residue Limits) procedures
- Consumer safety in MAA (Marketing Authorisation Applications) procedures

Notions of residues and consumer safety



Veterinary medicines for food producing animals:
… from animal to people

⇒ **Consumer safety** needs to be ensured

When is consumer safety addressed?

Consumer safety is evaluated:

- during MRL (Maximum Residue Limits) procedures by CVMP

  What is a safe level of residues in food commodities for this substance?

  ⇒ *MRL*

Scope:
Consumer safety

- during MAA (Marketing authorisations applications) procedures

  When is this safe level of residues reached for this product?

  ⇒ *Withdrawal period*

Scope:
- Quality
- Safety
  - Target animal
  - User
  - **Consumer**
  - Environment
- Efficacy

MRL procedures

- Definition of MRL:

  "Maximum concentration of a residue of a pharmacologically active substance which may be permitted in food of animal origin"

  [Regulation (EC) No 470/2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin […]]

Principles and objectives of MRLs

- Ensure consumer safety

  - MRLs must be set at a level which is safe for the consumer. MRLs setting is based on safety data and residue data.

  - MRLs are used to establish withdrawal periods within marketing authorisation procedures (residues ≤ MRL)

  - MRLs are used for residue surveillance by Member States (measured residues ≤ MRL)

- Facilitate trade within EU: avoid barriers to free movement of foodstuffs of animal origin between Member States

Regulatory and procedural aspects of MRLs

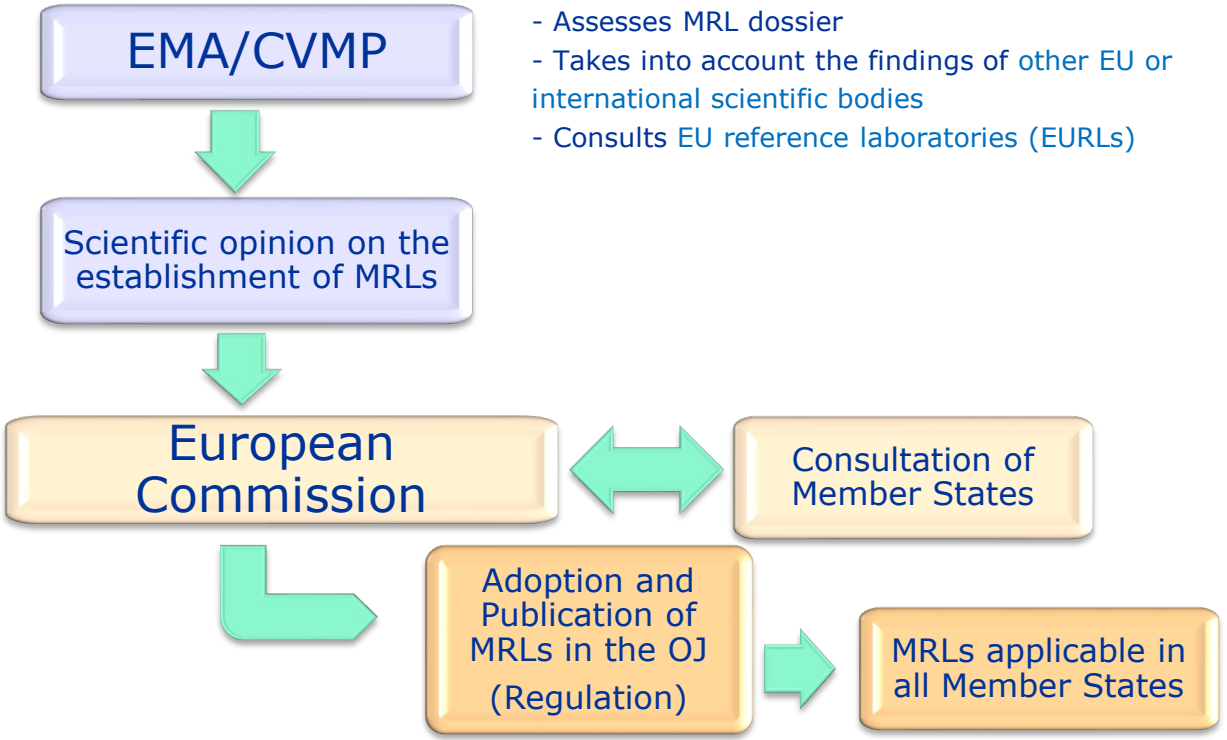
- An application for establishment of MRLs is a stand-alone, *centralised* procedure – not part of an application for a MA

  ⇨ Scientific evaluation for all MRL applications are performed by CVMP

- Establishment of MRLs is a pre-condition for marketing authorisation for veterinary medicinal products for food producing animals (if no MRLs established for pharmacologically active substance, no such marketing authorisation)

- MRL process has similarities with MAA evaluation

Establishment of MRLs in the EU



Possible outcomes of the evaluation

- Positive opinion ⇨ List of allowed substances (*Table 1* of Annex to Regulation 37/2010 on pharmacologically active substances and their classification regarding MRLs in foodstuffs of animal origin.)
  - Numerical MRLs established
    - *'x µg/kg'*

  OR

  - Numerical MRLs not required for protection of public health
    - *'No MRL required'*

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 20 µg/kg	Fat Liver	NO ENTRY	Anteparasitic agentes/Agenes aceing againte endo- and ecoparasitees
		Ovine	20 µg/kg 50 µg/kg 25 µg/kg 20 µg/kg	Muscle Fat Liver 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
Aceryl cysteine	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

Possible outcomes of the evaluation

- Negative opinion ⇨ List of prohibited substances (*Table 2* of same regulation)
  - MRLs not established because any presence of residues may constitute hazard to human health, or because no final conclusion concerning the effect on human health can be drawn

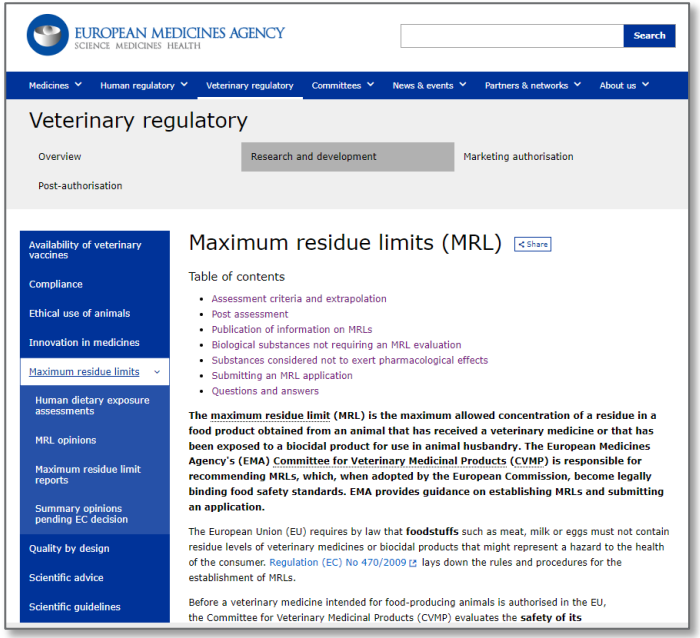
Table 2

Prohibited substances

	Pharmacologically active substance	MRL
	Aristolochia spp. and preparations thereof	MRL cannot be established
	Chloramphenicol	MRL cannot be established
▼M32	_____	
▼B		
	Chlorpromazine	MRL cannot be established
	Colchicine	MRL cannot be established
	Dapsone	MRL cannot be established
	Dimetridazole	MRL cannot be established
	Metronidazole	MRL cannot be established
	Nitrofurans (including furazolidone)	MRL cannot be established
	Ronidazole	MRL cannot be established

Information on MRLs made publicly available by the EMA

- Information is available on the Agency's website, and can be accessed from the MRL page
  - ✓ Procedural aspects
  - ✓ Outcome of MRL assessments:
    - European Public MRL Assessment Reports (EPMARs)…
  - ✓ Scientific guidelines
- Note: See also Implementing Regulations amending Regulation 37/2010 (OJ)



Residue surveillance

- EU countries implement control plans for residues of pharmacologically active substances:
  - Controls are carried out by Member States. EMA not involved.
  - Monitoring includes unauthorised substances, veterinary medicines, contaminants
- Consolidated report by EFSA: Report for 2021 on the results from the monitoring of veterinary medicinal product residues and other substances in live animals and animal products (wiley.com)
  - In 2021: 351,637 'targeted samples', 0.24% non-compliant

Consumer safety assessment in marketing authorisations

- Consumer safety based on:
  - ✓ MRL classification of each constituent.

    Each active substance and excipient in medicinal product for food producing animals needs to have an MRL classification

  - ✓ Withdrawal period of the veterinary medicinal product, if needed

Withdrawal period

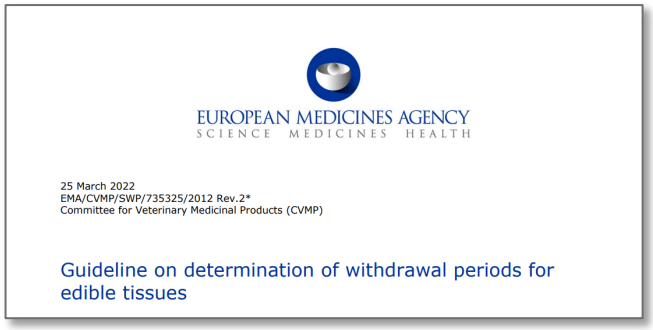
- "Withdrawal period means the minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that such foodstuffs do not contain residues in quantities harmful to public health"

  [Regulation 2019/6 on veterinary medicinal products and repealing Directive 2001/82/EC]

- Example:

  Cattle Meat and offal: 14 days Milk: 7 days

- Established on the basis of residue depletion studies, in accordance with relevant guidelines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25 March 2022
EMA/CVMP/SWP/735325/2012 Rev.2*
Committee for Veterinary Medicinal Products (CVMP)

Guideline on determination of withdrawal periods for edible tissues

Recent and on-going developments on MRL (1/2)

- Biological substances not requiring an MRL evaluation

The standard MRL procedure has been used for both 'chemical' and biological (non-immunological) substances. However, there was a need for a lighter procedure for some biological substances.

⇒ Application to assess the need for MRL evaluation. CVMP assesses the scientific basis provided. If there is no need for MRL evaluation, the substance is included in the ad-hoc list published by EMA.

[see Regulation (EU) 2018/782, Annex I, I.6 and I.7.]

First application received in 2019. List of biological substances not requiring an MRL evaluation published on the Agency's website since 2020.

Recent and on-going developments on MRL (2/2)

- Assessment of consumer exposure

The model used so far by CVMP to estimate consumer chronic exposure to residues is the TMDI (Theoretical Maximum Daily Intake) based on a standard food basket.

Some more complex models based on food consumption surveys are used by other organisations (EFSA, JECFA).

A joint working group under EC mandate has elaborated recommendations for harmonisation between sectors – published January 2023.
Assessment of human dietary exposure to residues of veterinary medicines in the EU | European Medicines Agency (europa.eu)

Work will continue based on these recommendations.

Conclusion

- Consumer safety is an important point to consider for medicines for food producing animals: veterinary medicines may leave residues in food from treated animals
- Consumer safety mainly relies on MRLs and withdrawal periods
- MRLs (i.e. maximum concentrations of residues permitted in food commodity) are established at EU level only and are directly applicable in all Member States
- MRLs ensure that consumption of the food basket is safe
- Withdrawal periods ensure that the residue in the food commodity does not exceed the MRL
- When assessing MRLs and consumer safety, EMA/CVMP contribute to **Public Health**

Thank you for your attention

Further information

Send a question to the European Medicines Agency | European Medicines Agency (EMA)

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Telephone +31 (0)88 781 6000 **Send us a question** Go to www.ema.europa.eu/contact

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