

Veterinary drug residues: The development and use of Maximum Residue Limits

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20 minutes



Scope of presentation

- Roles of EMEA, EFSA, Codex Alimentarius
- Terminology e.g. ADIs
- Relevant legislation
- Proposed changes to legislation
- Sources of further information



Setting of drug MRLs in the EU

- International committees of scientific experts set MRLs.
- In the European Union, the Committee for Medicinal Products for Veterinary Use (CVMP) assess safety data to set MRLs.
- The CVMP is part of the European Medicines Evaluation Agency (EMA)
- Additionally, the European Food Safety Authority sets MRLs for certain feed additives, such as coccidiostats.

Setting the Acceptable Daily Intake (ADI)

- Data from a wide range of short/long term experiments are studied.
- From these, the CVMP identify the quantity that had no adverse effect in any of the studies – the ‘No Observable Adverse Effect Level’ or NOAEL.
- This quantity is then divided by an uncertainty factor, typically 100-1000, to allow for possible differences between species/individuals and compensate for other uncertainties in the data.
- This quantity is the Acceptable Daily Intake, or ADI. This is the amount of a residue that is considered safe for a person to eat every day over a lifetime.



Setting Maximum Residue Limits (1)

- The ADI is divided among all the edible tissues where a substance is authorised (including honey and milk), taking account of:
 - how much of a particular food may be eaten each day
 - how much of the substance occurs in each food
 - how much the substance is changed in the animal's body
 - other possible sources of residues, as some substances are also used as pesticides or human medicines.



Setting Maximum Residue Limits (2)

- MRLs are set so that even if all of the foods contain residues at the respective MRLs, the ADI will not be exceeded.
- In practice, residues are not found in most foods that are tested.
- The upper quantities of foods that we are assumed to eat each day (based on a 60 kg person) are:
 - 100 g liver, 300 g muscle (muscle and skin for fish)
 - 50 g kidney, 50 g fat (fat and skin for pork and poultry)
 - 20 g honey
 - 1.5 litres of milk



Setting Withdrawal Periods

- The amount of a medicine or its residue in an animal will deplete over time as it is metabolised and excreted.
- The length of time that must elapse after the end of treatment with a medicine before that animal is slaughtered, or animal product is taken, for human consumption is the Withdrawal Period.
- It is set for each veterinary medicinal product that contains the active substance so that the residues in each food will be below the relevant MRL.

For further information on MRL guidelines see
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol8_en.htm



Further information on MRL guidelines

The rules governing medicinal products
in the European Union

October 2005

Volume 8

Notice to applicants and Guideline

Veterinary medicinal products

Establishment of maximum residue limits (MRLs) for
residues of veterinary medicinal products in foodstuffs of
animal origin

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol8_en.htm



Authorisation and use of veterinary medicines in Member States

- Directive 2001/82/EC
- Labelling rules
- Withdrawal periods
- Record keeping by farmer/vet/pharmacy/wholesaler
- Checks by the authorities



Council Directive 96/22/EC

- Stilbenes and thyrostats –
 - Must not be authorised for use in food producing animals
- Hormones and beta-agonists for growth promotion - total ban in EU for growth promotion, or
 - for Third countries a split system
 - several trading partners implement a 'split system'



Council Regulation (EEC) No 2377/90

Maximum Residue Limits (MRLs) for a wide range of pharmacologically active substances used in veterinary medicinal products.

- **Annex I** substances for which definitive MRLs have been established.
- **Annex II** List of substances not subject to maximum residue levels
- **Annex III** substances with provisional MRLs. Provisional MRLs are established, for a defined period of time
- **Annex IV** Lists of pharmacologically active substances for which no maximum levels can be fixed



Specific veterinary medicine issues for third countries (1)

- Stilbenes
- Thyrostats
- Hormones
- Beta-agonists
- Chloramphenicol
- Nitrofurans
- Some feed additives

Can **not** be used in any third country Art.11 Directive 96/22

Can be used in third country but only with 'split' system

Can be used in third country but no residues in food for EU

Residues not the main issue



Specific veterinary medicine issues for third countries (2)

Council Regulation (EEC) No 2377/90

- 'Annex IV' substances
 - e.g. chloramphenicol, nitrofurans, nitroimidazoles
 - Not obliged to prohibit use but if residues detected at import, Member States / Commission may act
 - MRPL - reference point for action
 - Community approach has been adopted by many trading partners
- Substances with no Community MRL (not in Annexes I, II, III)
 - Can be authorised in third country but zero tolerance applies for imported food in EU



Specific veterinary medicine issues for third countries (3)

EU-banned feed additives

- No explicit legal basis for EU to demand that these are not used in third country
- Residues not always the issue - transfer of antimicrobial resistance
- Some residues are of concern e.g. carbadox
 - How does a third country demonstrate **equivalence** with Community standards? -Monitoring? Split system? **Objective: freedom from residues in exports**



Substances tested in Member States

■ Group A

- A1 stilbenes
- A2 thyrostats
- A3 steroids
- A4 zeranol
- A5 beta-agonists
- A6 Reg 2377/90 Annex IV

■ Group B

- B1 antimicrobials
- B2a anthelmintic agents
- B2b coccidiostats
- B2c carbamates/pyrethroids
- B2d sedatives
- B2e NSAIDs
- B2f others e.g. corticoids
- B3a OCs, PCBs, dioxins
- B3b organophosphates
- B3c heavy metals
- B3d mycotoxins
- B3e dyes

Substances tested in third countries (1)

■ Group A

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- B2d sedatives
- B2e NSAIDs
- B2f others e.g. corticoids
- B3a OCs, PCBs, dioxins
- B3b organophosphates
- B3c heavy metals
- B3d mycotoxins
- B3e dyes

Mainly
Essential

Annex IV

Substances tested in third countries (2)

■ Group A

- A1 stilbenes
- A2 thyrostatics
- A3 steroids
- A4 zeranol
- A5 beta-agonists
- A6 Reg 2377/90 Annex IV

■ Group B

- B1 antimicrobials
- B2a anthelmintic agents
- B2b coccidiostats
- B2c carbamates/pyrethroids
- B2d sedatives
- B2e NSAIDs
- B2f others e.g. corticoids
- B3a OCS, PCBs, dioxins
- B3b organophosphates
- B3c heavy metals
- B3d mycotoxins
- B3e dyes

Justifications for omission (1)

- Group A substances: non-negotiable in most cases
- Exceptions include:
 - Group A3 (steroids) in shrimp
 - Group A2 (thyrostats) in poultry
- Some Group B are non-negotiable
 - Group B1 (antimicrobials) in all species
 - Group B3e (dyes e.g. malachite green) in finfish and shrimp



Justifications for omission (2)

- low chemical risk -
 - Could be reasonable argument;
- little likelihood of use / abuse in a specific sector -
 - could be a strong argument e.g. extensive systems;
- lack of product authorisation –
 - not necessarily a strong argument. For some substances (e.g. hormonal growth promoters) such a situation may encourage illegal imports and their illegal use. However, for other substances (e.g. coccidiostats) these would be very unlikely to be used in beef cattle, even if authorised.



Justifications for omission (3)

- historical residue monitoring information
 - a strong argument provided that the methods of analysis were sufficiently sensitive and capable of detecting abuse. Supporting documentation could include data (or trend analysis) of medicines records monitoring on farms.
 - FVO experience is that the volume and pattern of use of substances in different livestock groups is one topic about which third countries have very little information. Consequently in the absence of historical residue monitoring data, it can be difficult to estimate likely exposure of consumers to certain residues.



Future changes to Legislation (1)

Commission “Reflections” exercise

- Commission consulted stakeholders in 2004 on changes to EU legislation;
- General response was that surveillance should be based more on risk;
- Commission has produced draft legislation replacing Council Regulation 2377/90;
- Proposals to replace Council Directive 96/23/EC expected in 2009.

See http://ec.europa.eu/food/food/chemicalsafety/residues/reflection_en.htm



Future changes to Legislation (2)

Commission “Reflections” exercise Proposed Replacement of Council Regulation 2377/90

- Adopt new Codex MRLs as EU MRLs without further risk assessment where EU agrees science;
- More use of extrapolation where the science underpinning the original MRL is robust;
- Set Reference Points for Action for substances which cannot be used as Veterinary Medicinal Products



Further information

- **Community legislation**

- <http://europa.eu.int/eur-lex/lex/en/index.htm>

- **EudraLex - Volume 5 - Pharmaceutical legislation
Medicinal Products for veterinary use**

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol5_en.htm

- **Consolidated MRL list (Summary of amendments to Council
Regulation, 2377/90)**

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-5/reg_1990_2377_cons_2008/reg_1990_2377_consol_en.pdf

- **Online EU MRL database**

- www.fc24.eu

