



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

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Topics of presentation

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



European Medicines Agency - EMEA

- Responsible for the centralised (or Community) authorisation procedure.
 - *scope is set out in Annex 1 of regulation (EC) No 726/2004*
- Other procedures exist for veterinary medicines that do not fall with in the mandatory scope of the centralised procedure
 - *national, decentralised and mutual recognition procedures*
- Other functions of the EMEA include;
 - *communications to the public*
 - *promoting availability of veterinary medicines*
 - *continuously monitoring and assessing safety of vet medicines*
 - *recommending maximum residue limits (MRLs)*

Setting of drug MRLs in the EU



MRL- the maximum acceptable concentration of medicinal residues in food produced from treated animals

- International committees of scientific experts set MRLs.
- In the European Union, the Committee for Medicinal Products for Veterinary Use (CVMP – within EMEA) assess safety data to set MRLs.
- Additionally, the European Food Safety Authority sets MRLs for certain feed additives, such as coccidiostats.

http://www.efsa.europa.eu/EFSA/ScientificPanels/efsa_locale-1178620753812_FEEDAP.htm

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.

<http://www.vet-residues-committee.gov.uk/Reports/vrcar2008.pdf>

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

Further information on MRL guidelines



The rules governing medicinal products in the European Union

October 2007

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 2009/53/EC (18th June 2009) amending 2001/82/EC
- Labelling rules
- Withdrawal periods
- Record keeping by farmer/ vet/pharmacy/wholesaler
- Checks by the authorities



Directive 2008/97/EC, amending Council Directive 96/22/EC



- Stilbenes and thyrostats
- must not be authorised for use in food producing animals
- Hormones and beta-agonists - total ban in EU for growth promotion,

but
- Third countries can operate a split system (several trading partners do implement a 'split system')

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:318:0009:0011:EN:PDF>
<http://www.vet-residues-committee.gov.uk/Papers/Papers09/VRC0908.pdf>

European Community legislation for veterinary drug residue monitoring



- Legislation is established under;
 - Council Directive 96/23/EC
 - Commission Decision 97/747/EC
 - ~~Council Regulation 2377/90~~
- and more recently*
 - Council Regulation 470/2009 (repealing No 2377/90 and amending 2001/82/EC and No 726/2004)

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:152:0011:0022:EN:PDF>

Council Regulation 470/2009/EC ^(a)



Key points:-

- MRLs for authorised pharmacologically active substances
(Replacement of Annex 1 to 4 system in 2377/90)
- Scientific risk assessment ^(b) for
 - Reference Points for Action (RPA)
 - Extrapolation
- Adopt new Codex MRLs as EU MRLs without further risk assessment where EU agrees science;
- Pharmacologically active substances in biocidal products

(a) See http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf
(b) European Food Safety Authority (<http://www.efsa.europa.eu>)

Reference points for action (RPAs)



- When deemed necessary (*in accordance with Regulation No 882/2004*) the Commission may establish RPAs for pharmacologically active substances which are **not subject to a classification**
- The RPA should take into account the **lowest residue concentration** which can be quantified with a **validated** analytical method
- The principles of **risk assessment** shall be applied to guarantee a high level of protection of health

Extrapolation



MRLs established in a particular foodstuff for another foodstuff derived from the same species

OR

MRLs established for a pharmacologically active substance in one or more species for **other species**



Major to
minor species



Risk assessment and biocidal agents



Scientific risk assessment

- Metabolism and depletion of pharmacologically active substances in relevant animal species
- Type of residues that may be ingested over a lifetime
- Acceptable daily intake (ADI)
- Residues that occur in food of plant origin or come from the environment

Biocidal agents

- Antiseptics, disinfectants e.g. aldehydes, chlorhexidine salts, quaternary ammonium compounds, chlorine releasing agents, phenols etc.
- Pharmacologically active agents used in animal husbandry & technological aspects of food/feed production

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)



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 third countries (1)



Annexes I and II of 96/23/EC set out the groups veterinary residues that Member States are obliged to look for:

Group A	Group B
<ul style="list-style-type: none"> > stilbenes > thyrostats > steroids > zeranol > beta agonists > C0 compounds in Annex IV Council Regulation 2377/90/EC 	<ul style="list-style-type: none"> > antimicrobials > coccidiostats > anthelmintic agents > carbamates and pyrethroids > NSAIDs > organochlorines and PCBs > organophosphates > heavy metals > mycotoxins > dyes (including malachite green)

Mainly Essential

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Mainly Essential

Some Essential
Most Highly Desirable

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



Commission "Reflections" exercise

- Commission consulted stakeholders in 2004 on changes to EU legislation;
- General response was that surveillance should be based more on *risk*;
- **Council Regulation 2377/90 has been replaced**
- Proposals to replace Council Directive 96/23/EC expected in 2010.

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

Further information



- 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/mrl/regindex.htm>
- Online database for EU MRLs
www.fc24.eu

** expected soon: new COMMISSION REGULATION (EC) on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin
