Food Safety:
Legal issues related to Residues

Hugo Hays

"Sub-regional training course on veterinary legislation for OIE subject matter focal points in southern Africa"

Gaborone, 1-2 November 2011

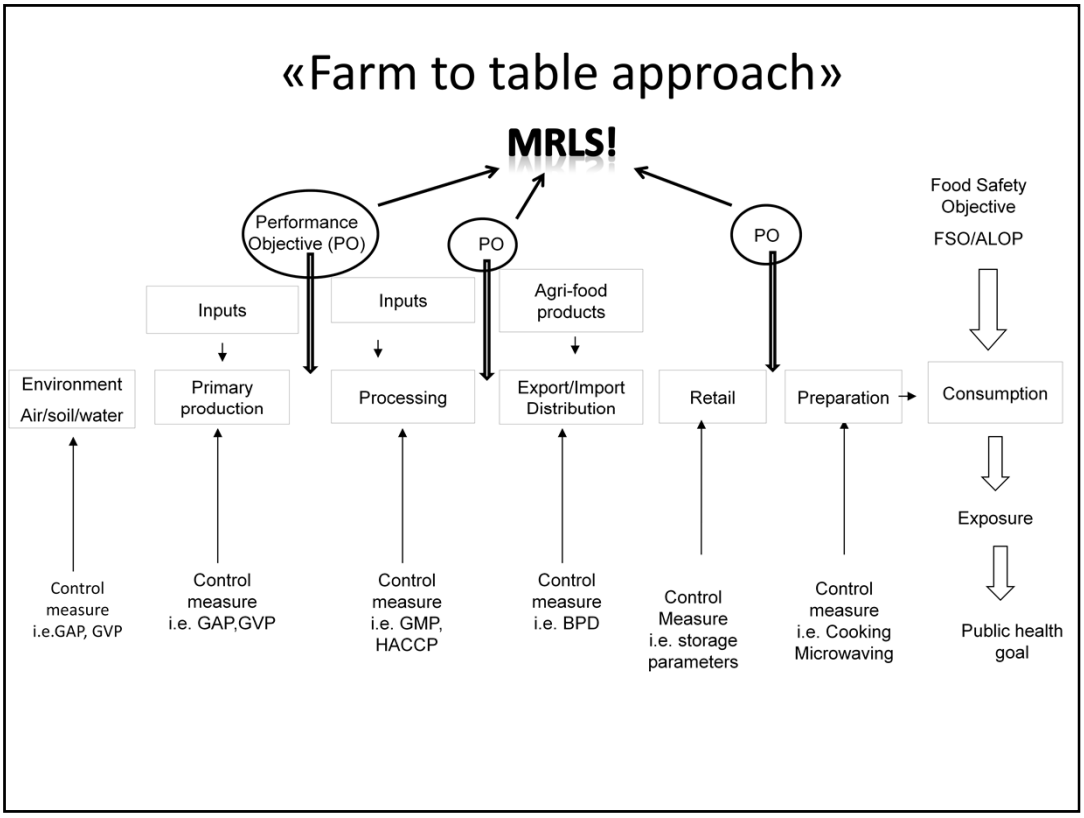
Contents

Introduction

1. Veterinary drugs/medicines are used to treat and prevent disease in animals, can enter the food chain. Some residues can come from environmental or feed contaminants.

1. Critically important that residues are NOT present in animals for consumption, (or minimally present so adverse effects on consumers cannot occur).

1. MRLs have therefore been set for the majority of animal remedies under Codex and national/regional legislations.



Remember that the responsibility for compliance lies with the Food Business Operator, and the responsibility for regulation and enforcement lies with the Authorities. Contractual issues also come into play, but are usually “food safety PLUS”.

Examples of Control measures:

1.Use of authorised Veterinary Medicines
2.Application of Vet. Medicines by authorised/trained personnel
3.Identification and tracing of animals
4.Respect for Withdrwawal periods
5.Hygiene aspects

Maximum Residue Levels result from Risk Analysis

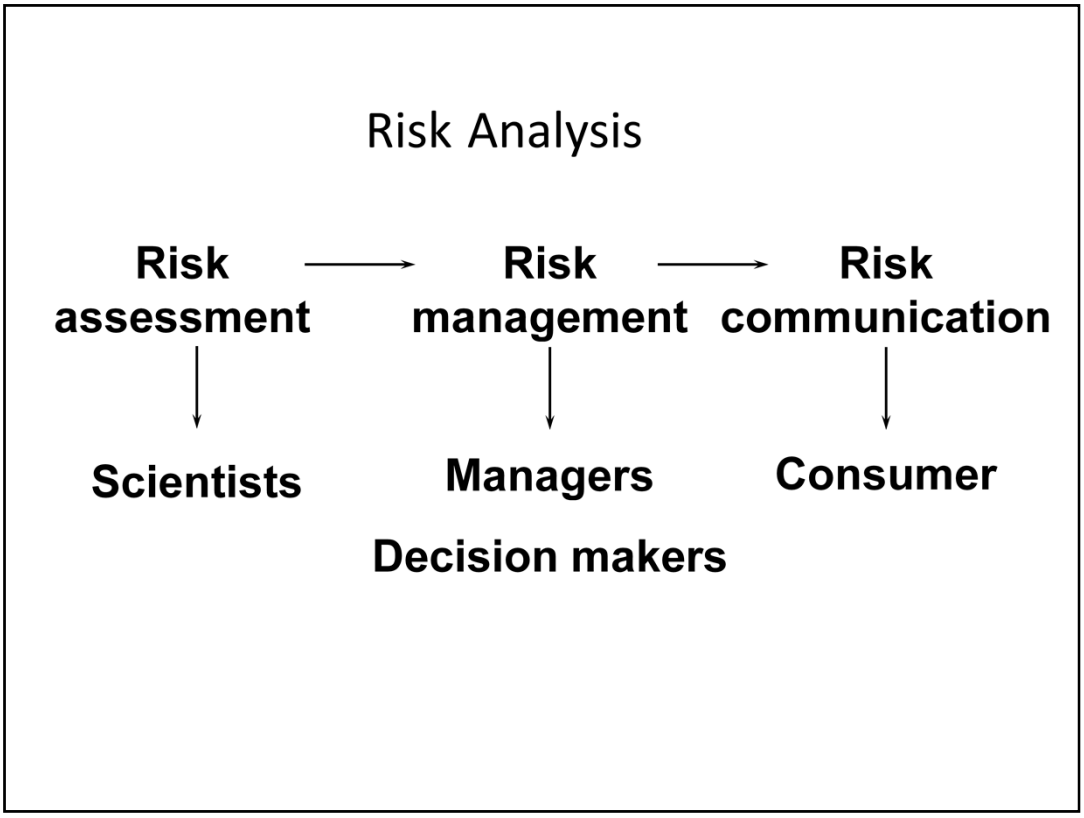
1. Food Risk Analysis: The basic principle of Food Safety
2. Identification of Hazards and their origin, and the Risk of their occurrence
   - Biological: pathogenic bacteria (Salmonella, E-Coli, Campylobacter), mycotoxins, viruses, prions
   - Chemical:
     Contaminants: dioxins, PCB's, heavy metals, POP's, endocrine disruptors, pseudo-estrogens,
     Residues: antibiotics, other veterinary drugs, pesticides
   3. Physical: glass, metal, plastic

1) MRLs are levels which must not be exceeded, for certain chemicals. In some cases: 0 MRL. So what is the basis that underpins MRL setting?

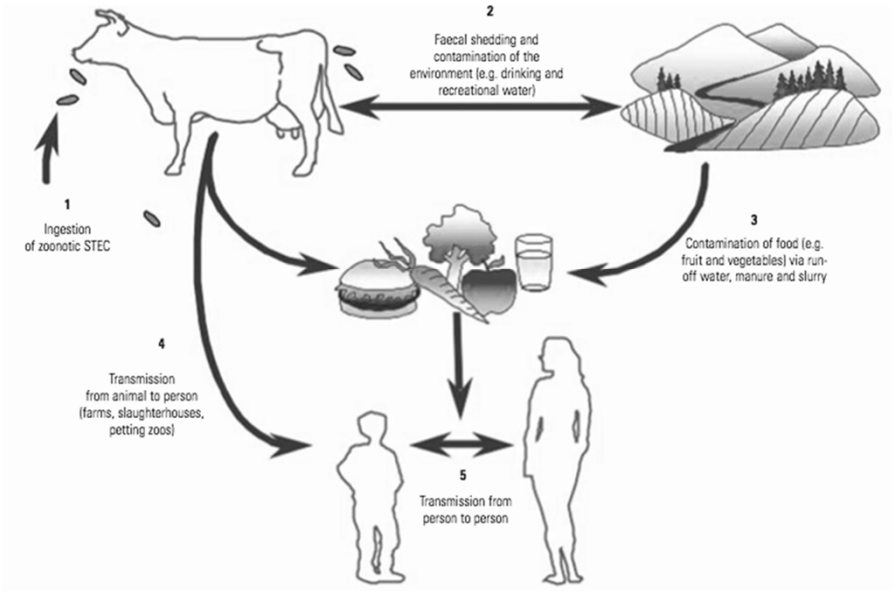
Risk Assessment

1) A structured and multidisciplinary approach to identifying and where possible, to reducing risk - Zero risk not achievable
2) Hazards. Long list of hazards, but is there a risk?

2) Hazard: A biological, chemical and physical agent in, or condition of a food, with the potentials to cause an adverse health effect
Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard in food


Risk Analysis
Risk assessment
Risk management
Risk communication
Scientists
Managers
Consumer
Decision makers

Example for E-Coli microbial contamination



Source: website of the Escherichia coli Laboratory (www.ecl-lab.ca)

Risk Assessment Steps

1. Hazard identification
   - What can the product do at any dose?
2. Hazard characterisation
   - What is the dose response?
   - What is the «safe» dose for humans?
3. Exposure assessment
   - What is the intake?
4. Risk characterisation
   - What the risk associated with the intake?

Mainly when we talk of MRLs it is linked to a specific chemical or family of chemicals.

Hazard Characterisation

Non Threshold effects	Threshold effect
• **Theoretical risk exist at any level**	• **Low level of intake exist without risk**
• **Mutagenicity**	• **Most forms of toxicity**
• **Genotoxicity**	
	• **ANALYSE TOXICITY**
• **WOULD NOT BE APPROVED**	• **DEFINE A SAFE INTAKE**

Mutagenicity: An agent, such as a chemical, ultraviolet light, or a radioactive element, that can induce or increase the frequency of mutation in an organism.
Genotoxicity: Genotoxins affecting sperm and eggs can pass genetic changes down to descendants who have never been exposed to the genotoxin.

Hazard Characterisation

- Threshold effect
  1. Analyse dose-response data to define the most sensitive toxic effect
  2. Define the daily dose that does not produce that effect (NOAEL= non-observed-adverse-effect-level)
  3. Divide the experimental dose by a safety factor to take into account interspecies extrapolation and human variability.
  4. The safety factor varies between 100 and 1000.
  5. ADI= NOAEL/100
  6. ADI is the acceptable daily intake that can be consumed daily over a life time without effect

Determining Acceptable Daily Intake (ADI)

1. Adverse systemic effect
2. Reproduction and developmental effect
3. Mutagenic effect
4. Carcinogenic effect
5. Effect on human intestinal flora
6. Immunologic effect
7. Pharmacological effect
8. Endocrine effect

Mutagenicity: An agent, such as a chemical, ultraviolet light, or a radioactive element, that can induce or increase the frequency of mutation in an organism.
Genotoxicity: Genotoxins affecting sperm and eggs can pass genetic changes down to descendants who have never been exposed to the genotoxin.

Determination of Acceptable Daily Intake

1. Studies on veterinary drugs in living organisms (metabolism studies) conducted in the food-producing animal (e.g., pigs, chickens, cows, goats, sheep, etc.)
2. Determination of duration for a drug and its metabolites to be excreted
3. Compare with similar studies done with laboratory animals
4. Toxicity of the substance is determined by toxicity, carcinogenicity (cancer) testing, based on the fact that the dose makes the poison.

Theoretical Maximum Daily Intake (TMDI)

- The TMDI is the sum of residue present in a food basket (daily consumption)
- The safe concentration of drug and its metabolites that could be consumed by individual eating the animal products
- Safe concentration= ADI x Body weight/Food Consumption Factor
- Example: 0,3kg of meat, 0,1kg of liver, 0,05kg fat, 0,05kg kidney, 1,5kg milk, 0,01kg eggs, 0,02kg honey.

Setting up MRL

1. An MRL is then set for the concentration of the drug residue remaining in the tissue sample
2. An analytical method is selected for the marker residue
3. The marker residue has a defined relation with the drug concentration
4. Residue depletion in animals based on the marker
5. A withdrawal period is then established based on the residue depletion data for the marker residue

EU as an example

- Animal remedies can be divided into 2 groups :
  - Unauthorised Substances, and
  - Veterinary Drugs and contaminants

Establishing MRLs: EU classification of Residues[1]

Group A – Substances having an anabolic effect and unauthorised substances

(1) Stilbenes, Stilbene derivatives, and their salts and esters
(2) Antithyroid agents
(3) Steroids
(4) Resorcyclic acid lactones including zeranol
(5) Beta-Agonists
(6) Other Compounds included in Annex IV to Council Regulation (ECC) No 2377/90

Group B – Veterinary drugs and contaminants

(1) Antibacterial substances, including sulphonamides and quinolones
(2) Other veterinary drugs
  (a) Anthelmintics
  (b) Anticoccidials, including nitroimidazoles
  (c) Carbamates and pyrethroids
  (d) Sedatives
  (e) Non-steroidal anti-inflammatory drugs (NSAIDS)
  (f) Other pharmacologically active substances
(3) Other substances and environmental contaminants
  (a) Organochlorine compounds including PCBs
  (b) Organophosphorous compounds
  (c) Chemical elements
  (d) Mycotoxins
  (e) Dyes
  (f) Others

[1]according to Annex 1 of Council Directive 96/23/EC

The number of animal remedies falling into Group A is relatively limited.

Ban on anabolic steroids for use in animals since 1986 in the EU. Beta Agonists have risen in use as a result – none approved by EU except Clenbuterol for certain uses.

Third countries:
1)And 2) cannot be used in any third country exporting to the EU
2)Hormones and Beta agonists can be used in third country only with a split system
3)Chloramphenicol and Nitrofurans can be used, but no residues must appear in the EU food

Group B contains a wide range of veterinary drugs, from different drug classes.
It includes common antibacterial drugs such as tetracyclines and penicillins, sedative drugs and growth promoters.

Substances in group B must be authorised for use by the respective national licensing body, usually following a centralised evaluation.

MRLs for food products result from calculations based upon the Acceptable Daily Intake (ADI). The ADI is the estimated amount (extrapolated from animal studies) of a residue which can be consumed daily over a lifetime without a health risk to the consumer.

Establishing MRLs

1. Consumers may consume residues when eating food derived from treated animals
2. Most drugs used in animal treatment are also used to treat disease in humans, where side effects of drugs at high doses are well-known.
3. Group B substances have an MRL set so that no health effects are anticipated in consumers.
4. Group A substances have potential health effects at any level, therefore no MRLs are established.
5. Spread of antibiotic resistance among bacterial species causing disease in humans linked to indiscriminate use of antibacterial drugs in food animals, leading to more stringent controls.

1) Such as meat from bovines, sheep, pigs and poultry, also farmed fish, milk, eggs and honey.
2) Residues of penicillin in slaughtered animals are considered a public health hazard because of the potential for hypersensitivity reactions in people.
3)
4) Steroids such as 17,- oestradiol are known carcinogens, both in animals and humans, and the nitrofuran group of drugs are also carcinogenic.
5) due to the demonstrated increase of antimicrobial resistance, the use of antibiotics as a feed additive was banned from 1 January 2006 in the EU, except those authorised as coccidiostats or histomonostats

Effects on Humans

Five Mexico stars banned after failing drugs test

From **Anisha Bhandari** and **Luis Arce**, CNN
June 10, 2011 -- Updated 1652 GMT (0052 HKT)

The five tested positive for clenbuterol, a banned anabolic agent that can be found in meats.

Mexican football officials contend the five players ingested the substance accidentally.

Overall, the effects of the ß-agonists are cardiac stimulation (increased heart rate, contractility, conduction velocity, relaxation) and systemic vasodilatation.

Alberto Contador blames tainted meat

Tour de France champion Alberto Contador's claim that the steak he ate is to blame for his positive doping test is plausible, experts say, since the drug he's accused of taking is sometimes illegally given to beef cattle.

1) Clenbuterol is an authorised ß-agonist for specific therapeutic uses in the EU (horses and cows) (3), USA (horses) (http://www.fda.gov/cvm/CVM_Updates/clenbut. htm), and Canada. In Australia, some ß-agonists, including clenbuterol, are authorised and their MRLs have been established.
2) Residues of penicillin in slaughtered animals are considered a public health hazard because of the potential for hypersensitivity reactions in people.

Legislation and Enforcement

1. Legislation should be developed following the "*OIE Guidelines on veterinary legislation*"
2. Programmes for the control of residues of veterinary drugs should follow the "*Guidelines For The Design And Implementation Of National Regulatory Food Safety Assurance Programme Associated With The Use Of Veterinary Drugs In Food Producing Animals*" developed by Codex (CAC/GL 71-2009).
3. In the SADC Region, the "*SADC Regional Guidelines for the Regulation of Veterinary Medicines*" has been approved by Ministers of Agriculture on 14th July 2011.

Legislation and Enforcement (cont'd)

4. In order to verify compliance to MRLs, a national residue monitoring plan should be drawn up and implemented - this will include use of appropriate laboratories, sampling guides, performance of analytical methods, interpretation of results.
5. The responsibility for compliance with MRLs lies with the primary producers and processors of primary produce.
6. Infringements and penalties should be clearly set out and communicated.

Veterinarian taking urine samples for determining use of illegal substances in pigs (Hong Kong).

Legislation and Enforcement (cont'd)

7. The legislation should cover countries from which animal products are imported.
8. The Enforcement Agency for compliance to MRLs must be legally mandated
9. The principal means of enforcement will be through sampling, following the Residue Monitoring Plan, which will be implemented at both farm and primary processing plant levels.
10. Sampling plans should follow criteria designed to target animals or products with higher risk of containing illegal residues, but also suspect animals detected at ate- or post-mortem inspection.
11. Sampling will also be conducted in specific cases where the presence of illegal residues is suspected by inspectors, for example, following ante or post-mortem examinations in slaughterhouses.
12. Residue breaches should lead to follow-up investigations at the farms of origin with a view to taking enforcement measures up to and including legal action, where appropriate.

10) Suspect animals are detained from entering the food chain and should they prove positive, they are then excluded.

Guidelines Available

1. CODEX code for minimising anti-microbial resistance RCP 61-2005
2. CODEX code for reduction of Dioxins in feeds RCP 62-2006
3. CODEX code hygienic practice for eggs RCP 15-1976
4. CODEX Code of hygiene for Fish & Fish prods RCP 52-2003
5. CODEX Code of hygiene for Meat RCP 58-2005
6. CODEX Code of hygiene for milk and milk products
7. CODEX guide for Good Animal Feeding Practices RCP 54-2004
8. Ecoli on-farm contamination animals OIERev08-fairbrother555-569
9. FAO Capacity Building on Good Animal Welfare practices
10. FAO Guide to Good Dairy Farming practices 2004
11. FAO-Carrefour Good Practices Meat Industry.
12. OIE Guide Good Farming Practices animal production-FS OIE-CODEX.
13. OIE standard for animal welfare 2005

10) Suspect animals are detained from entering the food chain and should they prove positive, they are then excluded.

Monitoring and Sampling

1. Sampling Plans should set out detailed rules on official sampling for the monitoring of substances and residues thereof in live animals and animal products.
2. The national plan should cover all farmed food-producing species.
3. Minimum levels and frequency of sampling should be laid down, and depend upon the species, matrix, analyte and number of animals slaughtered in the previous period.
4. The strategy should aim to a) detect all illegal treatments b) control the compliance with MRLs, and c) survey the reason for occurrence of
5. Official sampling should be unannounced and vary the time of sampling. The samples should be taken over a range of points such as farms, slaughterhouses, dairies, border inspection posts, etc. There should be mechanisms for self monitoring
6. Countries from which animal product imports are authorised should be listed, and criteria for inclusion set out.

1)
2) including fish, horses and farmed deer as well as food commodities such as milk, honey and eggs

6) Criteria for inclusion in the list should cover that the exporting country should have a residue plan that sets out guarantees as regards the monitoring of residues. Compliance with the requirements of and adherence to the guarantees offered by the plans submitted by the exporting countries should be verified by means of checks.

Targeting Inspections

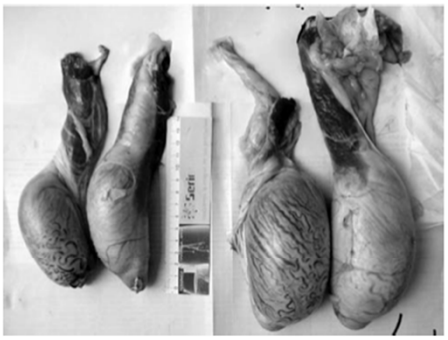


Fig. 3
Comparison between the testicles of one calf from the herd shown in Figure 2 and the testicles of another Holstein Friesian calf of the same age, from a different herd
The testicles on the left-hand picture show evident testicular atrophy

Source: Rev. sci. tech. Off. int. Epiz., 25 (2) 649

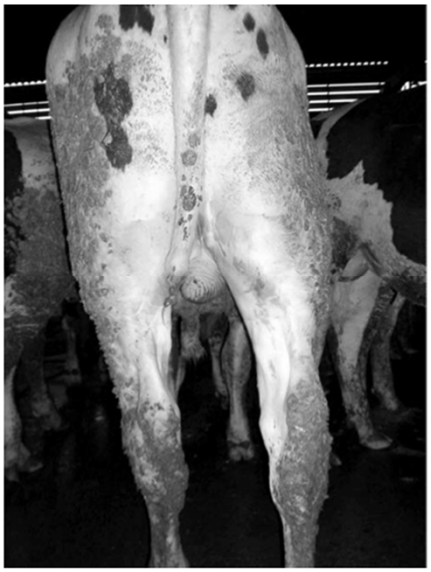


Fig. 2
A Holstein Friesian calf, aged eleven months, from a production unit of eight calves, of which seven showed testicular atrophy

1)

Targeting MRL exceedances/use of unauthorised substances

1. An evaluation of the Areas for Improvement and the Factors for Consideration should be carried out to try and improve monitoring and policing.
2. Control measures to avoid exceeding the MRLs of authorised substances, or the non-authorised use of legal substances, should be focused on the distribution of veterinary medicinal products, both at wholesale and retail level.
3. The most efficient measures to decrease illegal residues in food are those aimed at avoiding their use in the first place (at the farm level).
4. To ensure the correct administrative process and appropriate prosecution measures are followed, there should be effective feedback among laboratories, the police, health officials and prosecutors (e.g. sometimes a prosecution cannot be conducted due to an error in the administrative procedure)

1)

Evaluation of the Areas for Improvement and the Factors for Consideration

Area of improvement	Factors for consideration
Illegal trade ('black market') in illegal substances	– Food inspectors, agricultural departments, public prosecutor offices and police services should work together to improve the exchange of information and experience at European Union level – Black market networks operate in several countries. Illegal substances may be manufactured in one country, mixed with feed in another and finally illegally distributed to other Member States and third countries
Design of slaughterhouse facilities (to make ante- and post-mortem inspections easier)	Factors to be considered for identification and follow-up of any suspected carcass and its offal: – lighting – position and structure of lairage pens in relation to the position of the inspector – correct correlation of carcass with its offal – slaughterhouse facilities readily accessible to workstations for post-mortem inspections
Human resources	– Veterinary assistants are needed, to help inspectors with sampling, and identification and correlation of carcasses and offals. For instance, they can continue with the post-mortem inspection while the inspector investigates the presence of residues. – Scheduled slaughter times should be co-ordinated with inspection resources, especially during weekends and at nights – Palpation of both ears and other parts of the carcass should be conducted on every suspect animal (i.e. 100% of suspicious carcasses should be examined in this way
Further training needed for inspectors and farmers	– Periodical update of the trends for new substances and their effects on animals and carcasses – Some farmers may become confused about the legal use of some products from well-known companies (e.g. melengestrol acetate in the United States of America) since limitations on such use may depend on the species, sex and age of the animal

1)

Evaluation of the Areas for Improvement and the Factors for Consideration (cont'd)

Laboratory infrastructure necessary for a reliable residue control system	– Basic requirements are: accredited laboratories, appropriate analytical techniques for the various substances, recommended detection limits and validated methods – The list of available methods should be well disseminated and publicised by the competent authority – The results of the analytical methods should be consistent with the current authorised limits (e.g. a result indicating that a residue has been found at fewer than 15 parts per million (ppm) is not relevant if the maximum authorised limit is 2 ppm) – Better analytical techniques should be developed to improve the existing capacity to validate some illegal substances. Sometimes this is slower than producing and testing new substances for non-authorised use. Endogenous-like substances (such as 17-beta oestradiol) are more difficult to identify; thus, so are abnormal levels of these substances
Sampling at farm level (at production units suspected of infringement)	This is the most efficient way to follow up suspicious animals and conduct tests. Council Directive 96/23 provides that, for bovines, half the samples should be taken at farm level (16)
Legal advice should be sought at an early stage	To ensure the correct administrative process and appropriate prosecution measures are followed, there should be effective feedback among laboratories, the police, health officials and prosecutors (e.g. sometimes a prosecution cannot be conducted due to an error in the administrative procedure)
Technical facilities and communication systems should be available at the inspection point	To ensure effective communication: – telephone, e-mail, fax, digital cameras and intranet systems connecting all inspectors in all relevant regions should be available – all information should be shared with the appropriate research centres, government institutions and among slaughterhouse veterinarians

1)

Example EU 1992-93

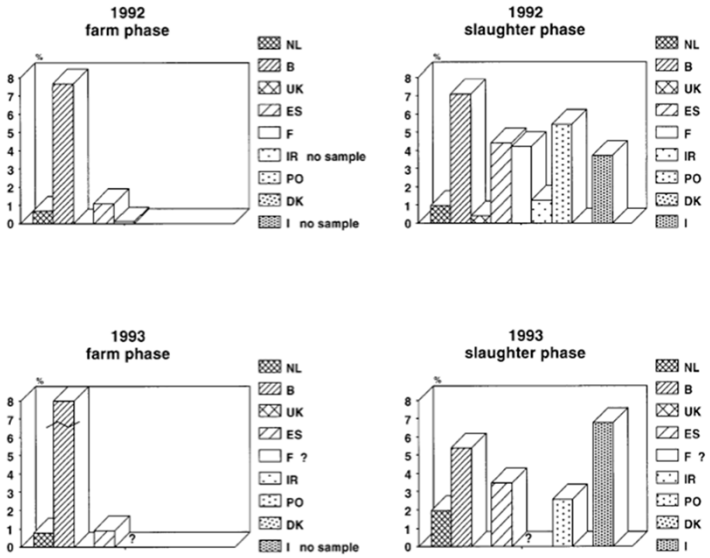
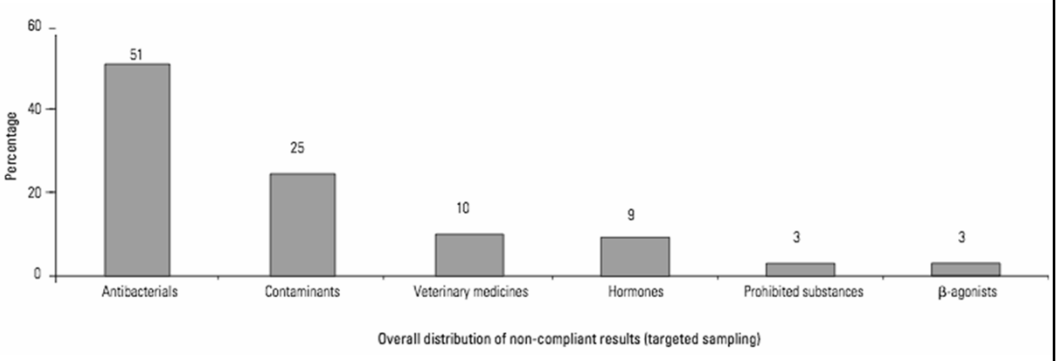


Figure 1. Percentage of random positive samples of bovine animals containing β-agonists in European Union Member States in 1992 and 1993 (European Commission). NL = The Netherlands, B = Belgium, UK = United Kingdom, ES = Spain, F = France, IR = Ireland, PO = Portugal, DK = Denmark, I = Italy.

High percentage of finds – RANDOM.

Example EU 2004



Overall distribution of non-compliant results (targeted sampling)

Approximately 807,000 targeted samples and 64,000 suspect samples were taken for the purpose of residue control by EU Member States in 2004 (6). These samples were taken from all food commodities, including bovines, pigs, horses, sheep and goats, poultry, milk, eggs, rabbit meat, game and honey.

In the national plan, Member States target the groups of animals and the sex/age combinations where the probability of finding residues is highest. This approach is different from random sampling, where the objective is to gather statistically significant data, for instance, to evaluate consumer exposure to a specific substance.

Suspect samples are those samples in the national monitoring plans taken as a consequence of:
a) non-compliant results on samples taken in accordance with the monitoring plan
b) the possession or presence of prohibited substances at any point during manufacture, storage, distribution or sale throughout the food and feed production chain
c) suspicion or evidence of illegal treatment or non- compliance with the withdrawal period for an authorised veterinary medicinal product.

0.12% of samples were non-compliant for hormones in cattle
0.3% of the results were non-compliant for hormones in pigs

The incidence of non-compliant samples increased from 0.02% of the bovines analysed in 2003 to 0.06% in 2004.

Analysis

1. General screening methods for veterinary drugs include 4 and 6 plate tests, ELISA, chromatography and biosensors.
2. For confirmation methods, chromatographic separation with spectrometric detection is essential. GC-MS and LC-MS are the methods of choice.
3. With improvements in interface technology, methods using LC-MS with electrospray ionisation (ESI) or Atmospheric Pressure Chemical Ionisation (APCI) interfaces are commonly used.
4. The standard to which the laboratories are accredited must comply with ISO 17025.

Responsibilities of Food Business Operators

1. FBOs have a general responsibility to supply safe food
2. Specific responsibility rests with farmers and processors of primary products to ensure that animals supplied or accepted do not contain harmful residues, and to ensure that they comply with MRLs of animal remedies
3. In addition to the official testing, primary processors in the red and white meat sectors and also in the milk sector should carry out residue testing.
4. Processors are required to submit annual residue monitoring plans to the authorities for approval. A progressively increasing scale of testing should be applied to suppliers of residue positive animals or milk.
5. A register must be kept on the farm where the date and nature of any treatment prescribed or administered is recorded, the identification of the animals treated and the corresponding withdrawal periods.

1) Individual (and unique) id becomes essential, as does a traceability system, once records are required.

Penalties

When the person (or persons) responsible for the presence of the residue in the food has been identified, and the breach of legislation proven, penalties can be imposed, including:

- fines
- loss of the ability to apply for aid for a period of 12 months
- cancellation of the farming licence
- sanctions against the veterinarian
- criminal sanctions against the person responsible, including jail.

After full investigation and proof of contamination.

Dr. administering Michael Jackson…

SADC Regional Guidelines for the Regulation of Veterinary Drugs

- **SADC Roles/Rules**
- **Development of Regional Guidelines**
- **Process for Developing Guidelines**
- **Content of Veterinary Drug Guidelines**

SADC Region: Basic roles/rules

- Only Member States can regulate in the countries in the SADC Region.
- SADC Secretariat can only advise on the best way to regulate/legislate.
- SADC Secretariat's role in regulation rests mainly in the harmonisation of legislation, following the principle of Regional Integration.
- The tools at the disposal of the Secretariat are the development of Regional Guidelines, Memorandums of Understanding (both voluntary) and Regional Protocols (which become compulsory once ratified).
- Regional Committees (such as the SPS Committee), which are composed of Member State representatives, oversee the implementation of Guidelines, MoUs and Protocols

Development of Regional Guidelines

- Involved an Inclusive Consultation Process:
  - 13 National SPS Workshops carried out Jan-May 2009
    - Analysing Strength Weakness Opportunity and Threats (SWOT)
    - Gaps of Member States' SPS related legislation
    - Management system with the participation of all stakeholders operating along the food chain
    - Laboratory analytical capacity (Pesticides, Veterinary Drugs residues, heavy metals, pathogens, …)

Process for Developing Guidelines

- The guidelines take into account provisions and general framework developed by international organisations such as the OIE and Codex
- The first drafts reviewed by SADC Member States during a Technical Workshop held in October 2009
- Member State Consultations: May 2010 to April 2011
- Submission and Approval to Ministers of Agriculture and Food Security in July 2011.

Content of Veterinary Drugs Guidelines

1. Scope Of The Veterinary Drugs And Products Guidelines
2. Introduction
3. Objectives Of The Veterinary Drugs Regulation Guidelines
4. Terms And Definitions
5. Regional Policy Guidelines
6. Context For The Design Of National Veterinary Drugs Legislation In The Sadc Region
7. Legislative Framework And Key Issues For The Sadc Region
8. A Proposed Framework For Registration And Quality Control Of Veterinary Drugs At National And Sadc Regional Level

Veterinary Drugs Guidelines Objectives

- The objective is to provide a general scientific framework including basic methodology, technical requirements, ethical principles as well as regulatory aspects to register veterinary drugs in SADC Member States
- Provide appropriate health care to animals
- Provide the regional market with drugs that have proven safety, efficacy and quality

Veterinary Drugs Guidelines Objectives (cont'd)

- Efficacy and quality
- Provide transparency in trade of agricultural products including animal and animal products within and outside the region
- Raise public awareness in the use of veterinary drugs
- Protect public health against *zoonotic* diseases

Veterinary Drugs Guidelines Objectives (cont'd)

- Protect the environment
- Provide the regulatory basis for management and control of veterinary drugs
- Provide a relevant approach for the observance and compliance with MRLs.

THANK YOU FOR YOUR ATTENTION

Further questions to:

hugohays@gmail.com