# Responsible Use of Veterinary Products

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## Pertinent International Resources

- Organization for Economic Co-Operation and Development (OECD)
- Understanding the Codex Alimentarius
- IPCS Principles and Methods for the Risk Assessment of Chemicals in Food
  - Chapter 8 MRLs for Pesticides and Veterinary Drugs

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## Pertinent International Resources

- CAC/ GL 71-2009 GUIDELINES FOR THE DESIGN AND IMPLEMENTATION OF NATIONAL REGULATORY FOOD SAFETY ASSURANCE PROGRAMME ASSOCIATED WITH THE USE OF VETERINARY DRUGS IN FOOD PRODUCING ANIMALS

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## Elements of a Successful Regulatory System

- Responsive
- Outcomes based
- Predictable
- Applies appropriate controls
- Independent

*NAS Institute of Medicine* Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad meeting notes 9/19/2012

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## OIE Guidelines on Veterinary Legislation

- 9.1 Veterinary legislation should address the following elements: i) avoiding the presence of harmful residues in the food chain; ii) ensuring that the use of veterinary products does not give rise to human health risk
- 9.3 ii) Veterinary legislation should address…establishment of the withdrawal periods and maximum residue limits for veterinary products as appropriate

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## General principles for evaluating safety of compounds in food producing animals

- Determine whether each food additive, new animal drug, or color additive proposed for use in food-producing animals is safe for those animals and whether the edible products derived from treated animals are safe.
- US EXAMPLE: Sponsor of the compound is required to furnish to FDA the scientific information necessary for demonstrating that the residues of the sponsored compound in the edible products of treated animals are safe.

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# U. S. EXAMPLE: Foodborne Surveillance

FSIS tests selected meat, poultry, and egg products for microbial hazards of public health concern


Voluntary data-gathering program which tests fresh fruit and vegetables for targeted foodborne pathogens and indicator organisms


Collaborative effort among FDA, USDA, and CDC which monitors antimicrobial susceptibility patterns of zoonotic enteric bacteria


Network of public health and regulatory labs that perform molecular subtyping of certain foodborne pathogens


Collaborative effort among CDC, USDA-FSIS, FDA, and participating state health departments

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# Definition of Residue:

- Any compound present in the edible tissues after treatment with a drug
- Includes parent drug, metabolites, and any substance formed in or on food

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## Definition of MRL

- Maximum concentration of residue resulting from the use of a veterinary drug that is set by the **Codex Alimentarius Commission** (CAC) to be legally permitted or recognized as acceptable in or on a food
- MRLs recommended by JECFA to the CCRVDF are expressed as concentrations of the marker residue

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## Definition of Marker Residue

- A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues
- JECFA uses residue depletion studies with radiolabelled parent drugs in target animals to determine the marker residue.

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## U. S. EXAMPLE: FDA Veterinary Drug Approval Process

- Veterinary drugs are evaluated for:
  - Effectiveness
  - Target Animal Safety
  - Environmental Safety
  - Chemistry, Manufacturing, and Controls
  - Labeling
  - Human Food Safety

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## Human Food Safety Evaluation

- Answers the question - When are the edible tissues from an animal treated with a drug safe for humans to consume?

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## Edible tissues for all food animals:

- Muscle
- Liver
- Kidney
- Fat/Skin
- Milk
- Eggs
- Honey

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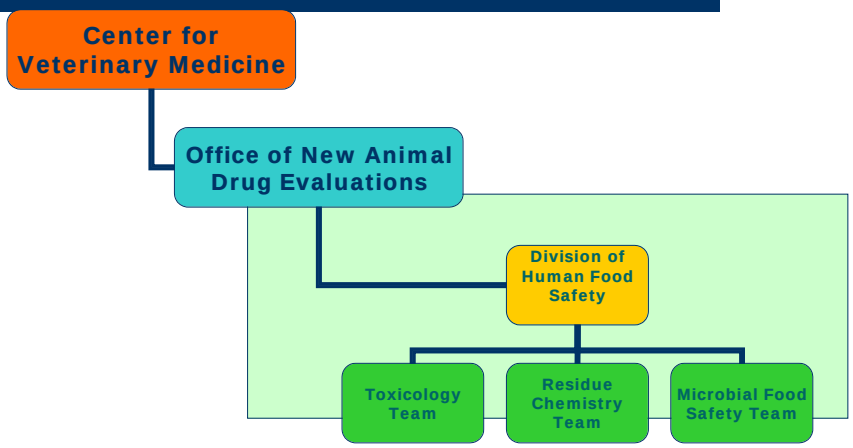
## U. S. Example: Organizational structure

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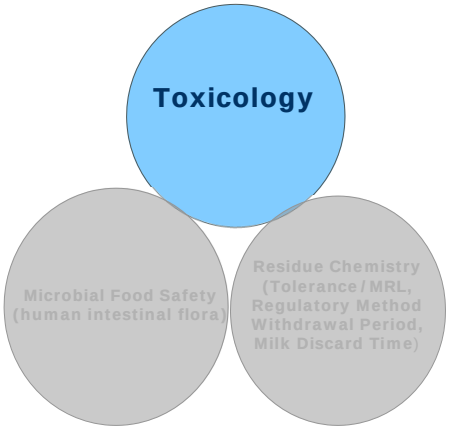
## Human Food Safety Assessment

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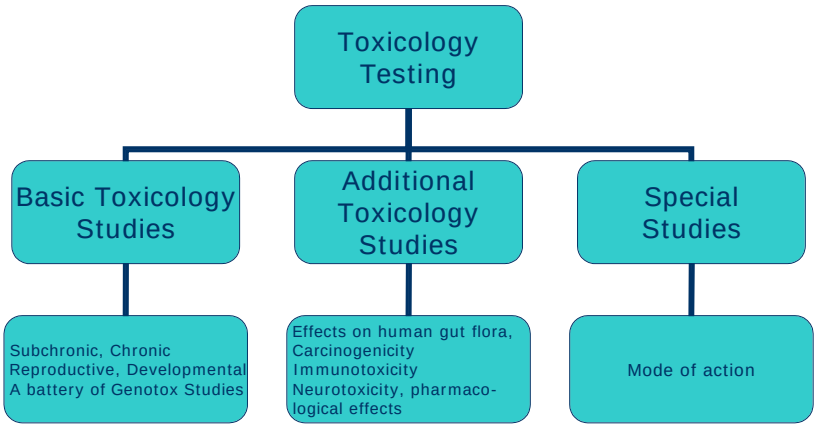
## Recommended Testing Approach

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## VICH Safety Guidelines Implemented as FDA/CVM Guidance for Industry (GFI)

| VICH GL# | | Subject |
|---|---|---|
| GL33 | GFI 149 | **General Approach to Testing** |
| GL31 | GFI 147 | **Repeat-Dose (90-day) Toxicity Testing** |
| GL37 | GFI 160 | **Repeat-Dose (Chronic) Toxicity Testing** |
| GL22 | GFI 115 | **Reproductive Toxicity Testing** |
| GL32 | GFI 148 | **Developmental Toxicity Testing** |
| GL23 | GFI 116 | **Genotoxicity Testing** |
| GL28 | GFI 141 | **Carcinogenicity Testing** |

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## Toxicology Testing

- Define the biological effect(s) of a compound and its quantitative limits
- All testing is conducted through oral exposure in surrogate laboratory species
- Tested substance: parent drug substance, its metabolite(s), excipient(s), or formulated drug product

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## Toxicology Assessment

- Identify and characterize any potential adverse health effects

Risk = Hazard X Exposure

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## Toxicology Assessment

The general approach is to

- Establish a human Acceptable Daily Intake (ADI) level for total drug residues in edible tissues based on toxicology testing
- ADI - An estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily *over a lifetime* without appreciable health risk (standard person = 60 kg)

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## Food Basket

- Assumption that all of each edible product is eaten each day for lifetime
- Estimated Daily Intake (EDI)
- Total radiolabeled residues for each edible tissue X food basket contribution to determine when total exposure will be below the ADI

| Edible Product | Food Consumption |
|---|---|
| Muscle | 300 g |
| Liver | 100 g |
| Kidney | 50 g |
| Fat (fat/skin) | 50 g |
| Eggs | 100 g |
| Milk | 1.5 L |
| Honey | 50 g |

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## Summary

- Toxicology human food safety assessment to identify and characterize any potential adverse health effects that may be caused by the consumption of drug residues in edible tissues of food-producing animals.
- As a result of toxicology human food safety assessment, a human ADI for total drug residues is assigned.

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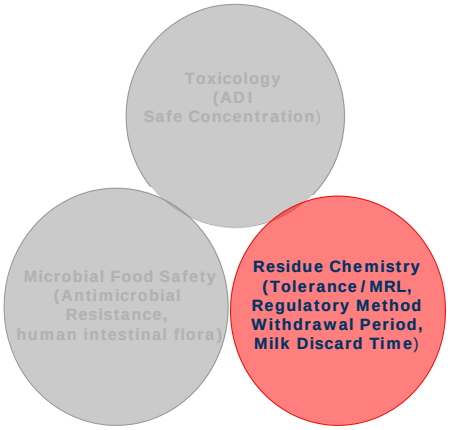
## Human Food Safety Assessment

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## Objective of Residue Chemistry Studies

How can the hazard identified in the toxicology or microbial food safety studies be mitigated?

Risk = Hazard X Exposure

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## Criteria for JECFA to recommend MRLs

- Veterinary drugs proposed for evaluation by JECFA should be
  - registered by national or regional authorities, commercially available with established label
  - used according to the Good Practice in the Use of Veterinary Drugs (GPVD)
- GPVD - officially recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions

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## Where are MRLs found?

- http://www.codexalimentarius.net/vetdrugs/data/index.html
  http://www.codexalimentarius.net/vetdrugs/data/MAS-RVDF_2006_e.pdf
- http://www.codexalimentarius.net/vetdrugs/data/vetdrugs/classes.html

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## Tissue Residue Depletion Study

Objective: Run a residue depletion study under field conditions and use the determinative method to measure how long it takes the marker residue to deplete to below the MRL

- determine the withdrawal period or milk discard time

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## Definition of Withdrawal Period/Milk Discard Time

- The time interval between the last administration of a sponsored compound and when the animal can be safely slaughtered for food or the milk can be safely consumed.
- The withdrawal period will appear on the product label

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## Tissue Residue Depletion Study

- Target food animals (usually market size)
- Dosed according to proposed product label
  - highest dose
  - longest duration of treatment
- Sample animals at timepoints after drug is withdrawn
- Collect and analyze tissues for drug residues

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## Residue Monitoring Plan

- GUIDELINES FOR THE DESIGN AND IMPLEMENTATION OF NATIONAL REGULATORY FOOD SAFETY ASSURANCE PROGRAMME ASSOCIATED WITH THE USE OF VETERINARY DRUGS IN FOOD PRODUCING ANIMALS CAC/GL 71-2009

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## Programmes for the control of residues of veterinary drugs in foods should:

- i. Be based on risk using realistic risk profiles assessed as reasonably likely to be associated with food derived from the relevant productions system(s)
- ii. Be prevention focused based on the realistic risk profiles associated with the probable or known use of approved, non-approved and prohibited veterinary drugs in the production system

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## Programmes for the control of residues of veterinary drugs in foods should:

- iii. Include regulatory measures proportionate to the relative human health risk associated with these hazards compared with other food-associated hazards
- iv. Ensure all parties involved in the production, marketing and processing system of the animals and/or the food products derived from them are held accountable to ensure that unsafe animal products will not be sold as a result of their action or inaction

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## Programmes for the control of residues of veterinary drugs in foods should:

- v. Recognise that pre-harvest controls and practices are the primary means for ensuring safe food
- vi. Recognise that the primary role of audits and sampling programmes is to verify the implementation and effectiveness of the pre-harvest controls and practices

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## Programmes for the control of residues of veterinary drugs in foods should:

- vii. Focus on system and population based assurances
- viii. Be cost effective and have the support of stakeholders

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