# Human Food Safety of Veterinary Drugs

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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

# 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

# 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

# Definition of Residue:

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

# Definition of MRL

- Maximum concentration of residue resulting from the use of a veterinary drug that is recommended by the Codex Alimentarius Commission 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

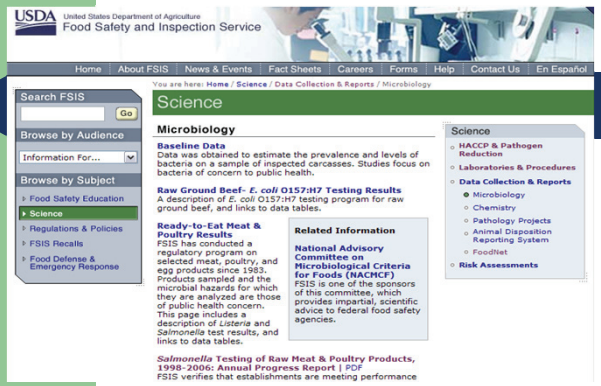
# Definition of Marker Residue

- A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues. A specific quantitative analytical method for measuring the concentration of the residue with the required sensitivity must be available.
- JECFA uses residue depletion studies with radiolabelled parent drugs in target animals to determine the marker residue

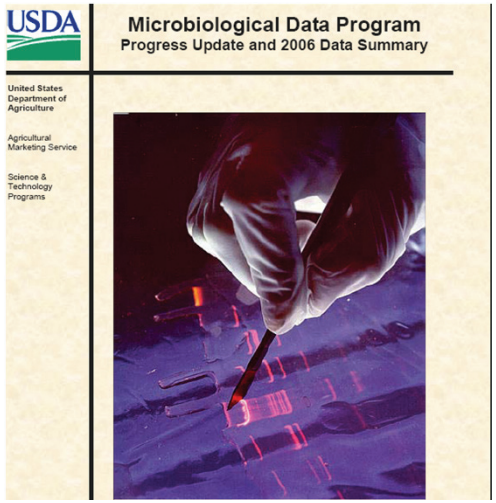
# General principles for evaluating safety of compounds in food producing animals

- 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.

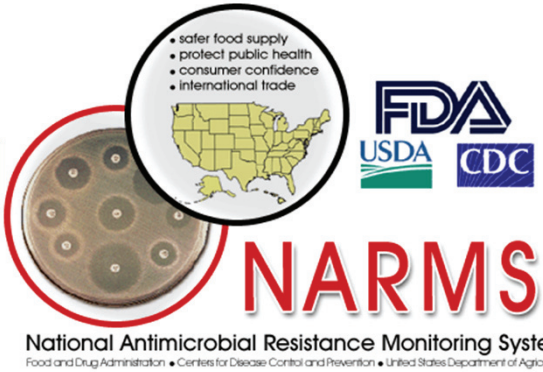
# U. S. EXAMPLE: Foodborne Surveillance



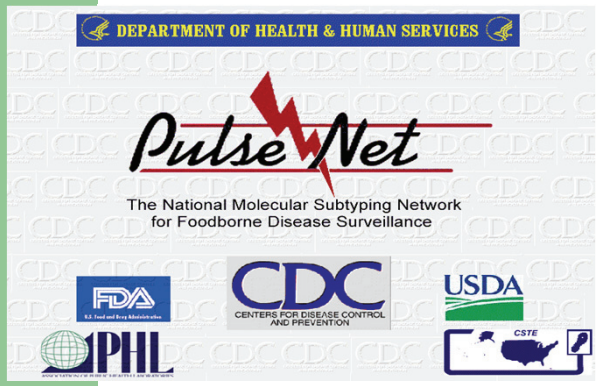

FSIS tests selected meat, poultry, and egg products for microbial hazards of public health concern




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

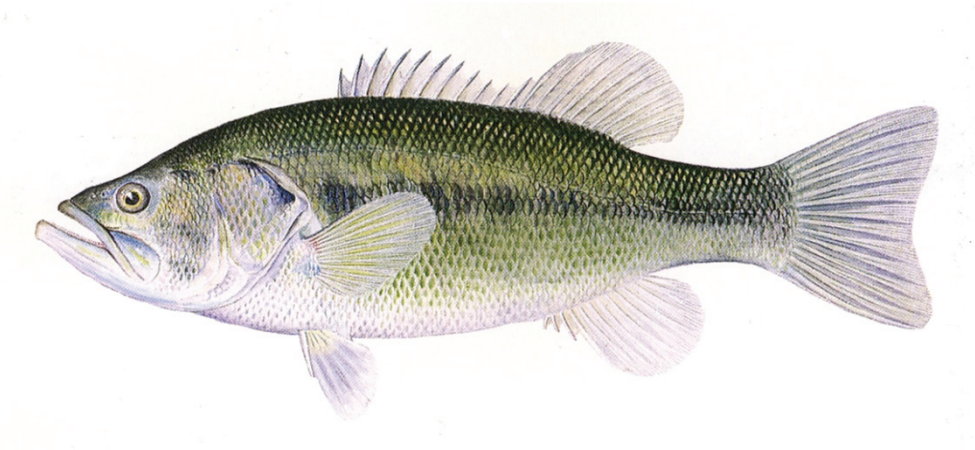

Collaborative effort among CDC, USDA-FSIS, FDA, and participating state health departments

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

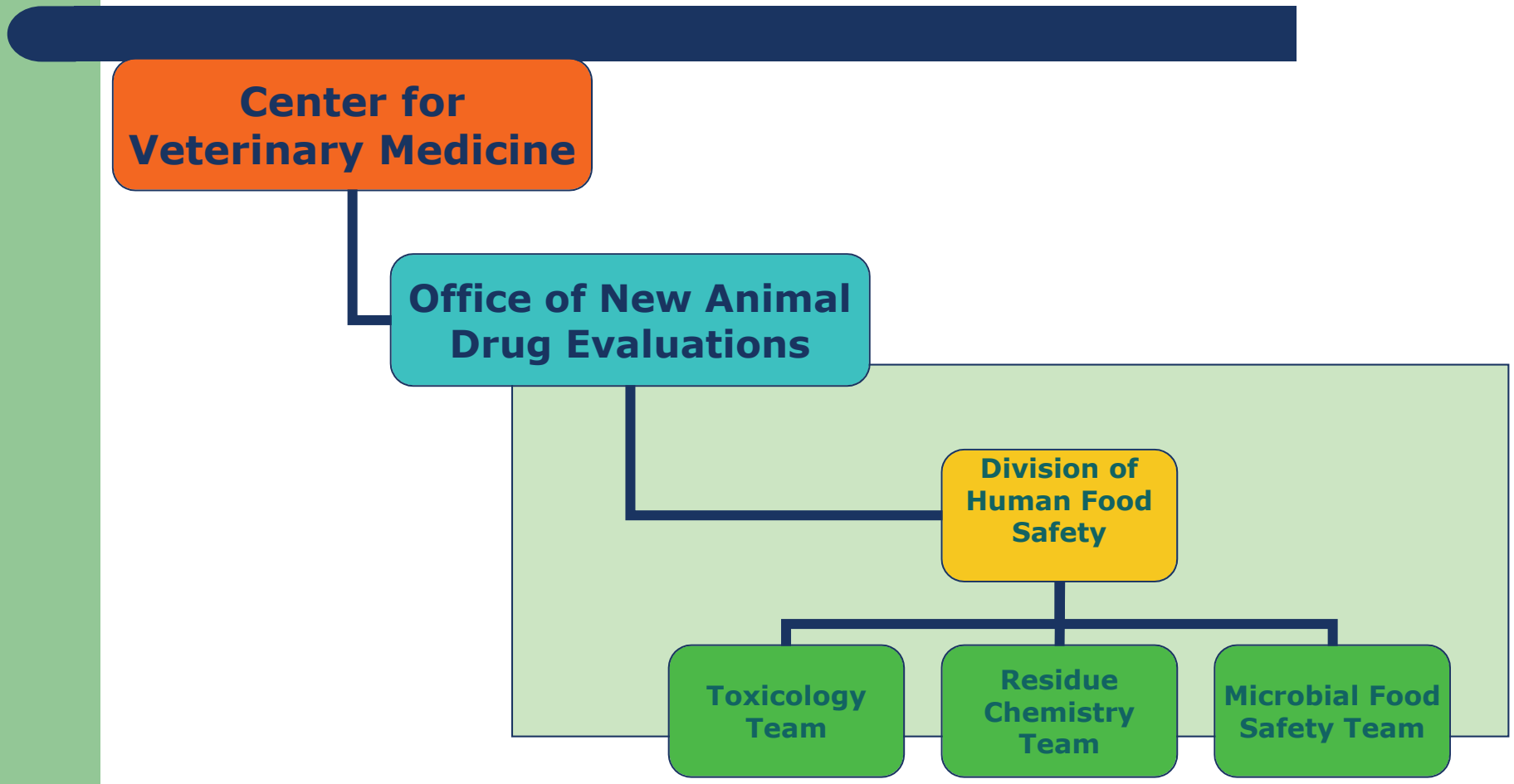
- Veterinary drugs are evaluated for:
  - Effectiveness
  - Target Animal Safety
  - Environmental Safety
  - Chemistry, Manufacturing, and Controls
  - Labeling
  - Human Food Safety

# Human Food Safety Evaluation

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



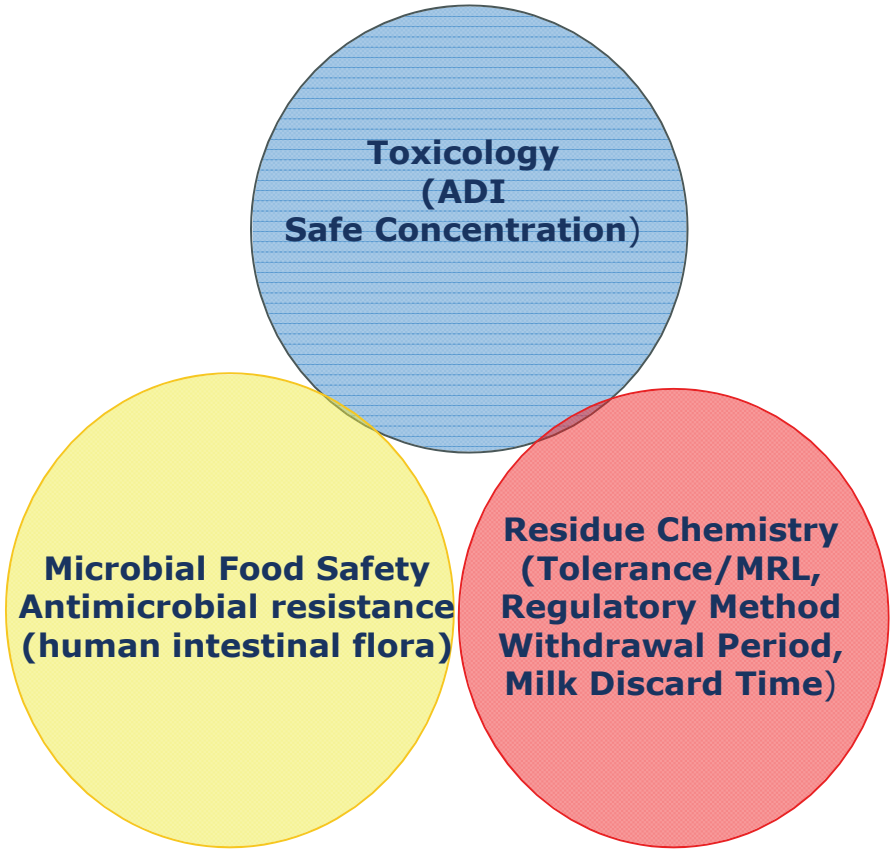
# U. S. Example: Organizational structure



# Edible tissues for all food animals:

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

# U. S. EXAMPLE: Human Food Safety Assessment



# 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** |

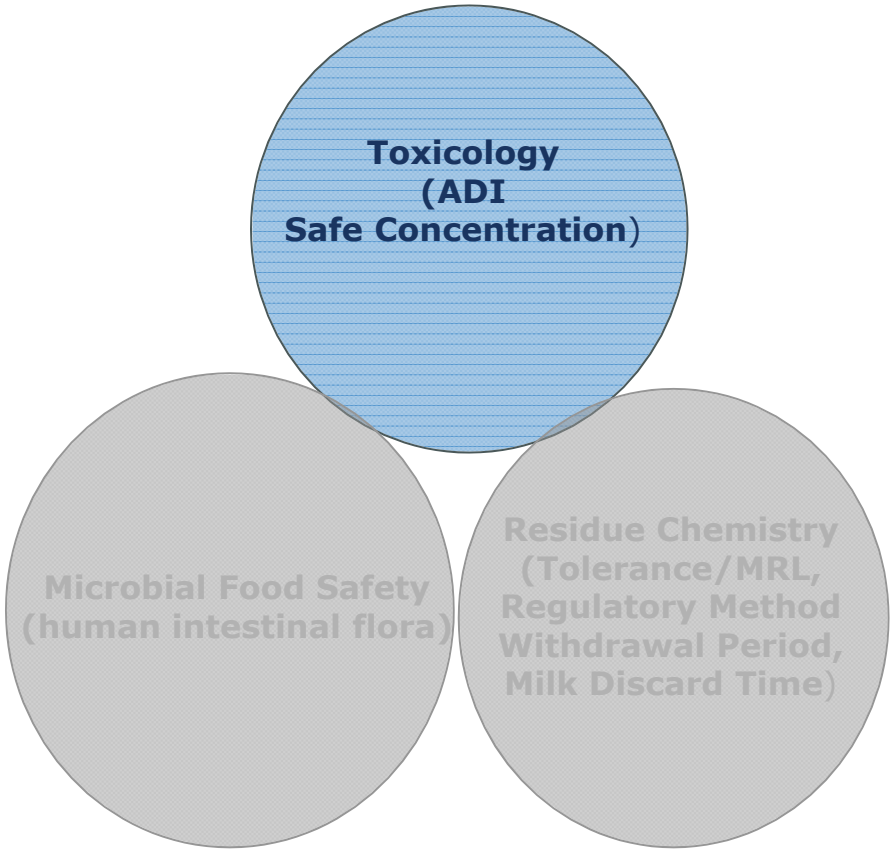
# VICH Safety Guidelines Implemented as FDA/CVM Guidance for Industry (GFI)

| VICH GL# | CVM GFI# | Subject |
|---|---|---|
| GL46 | GFI 149 | Metabolism Study to Determine the Quantity and Identify the Nature of Residues (MRK) |
| GL47 | GFI 147 | Comparative Metabolism Studies in Laboratory Animals |
| GL48 | GFI 160 | Marker Residue Depletion Studies To Establish Product Withdrawal Periods |
| GL49 | GFI 115 | Validation of Analytical Methods used in Residue Depletion Studies |

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

| VICH GL# | CVM GFI# | Subject |
|---|---|---|
| | GFI 152 | Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern |
| GL36 | GFI 159 | Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI |

# Human Food Safety Assessment



# Toxicology Assessment

- Identify and characterize any potential adverse health effects

Risk = Hazard X Exposure

# 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

# Toxicology Assessment

The general approach is to

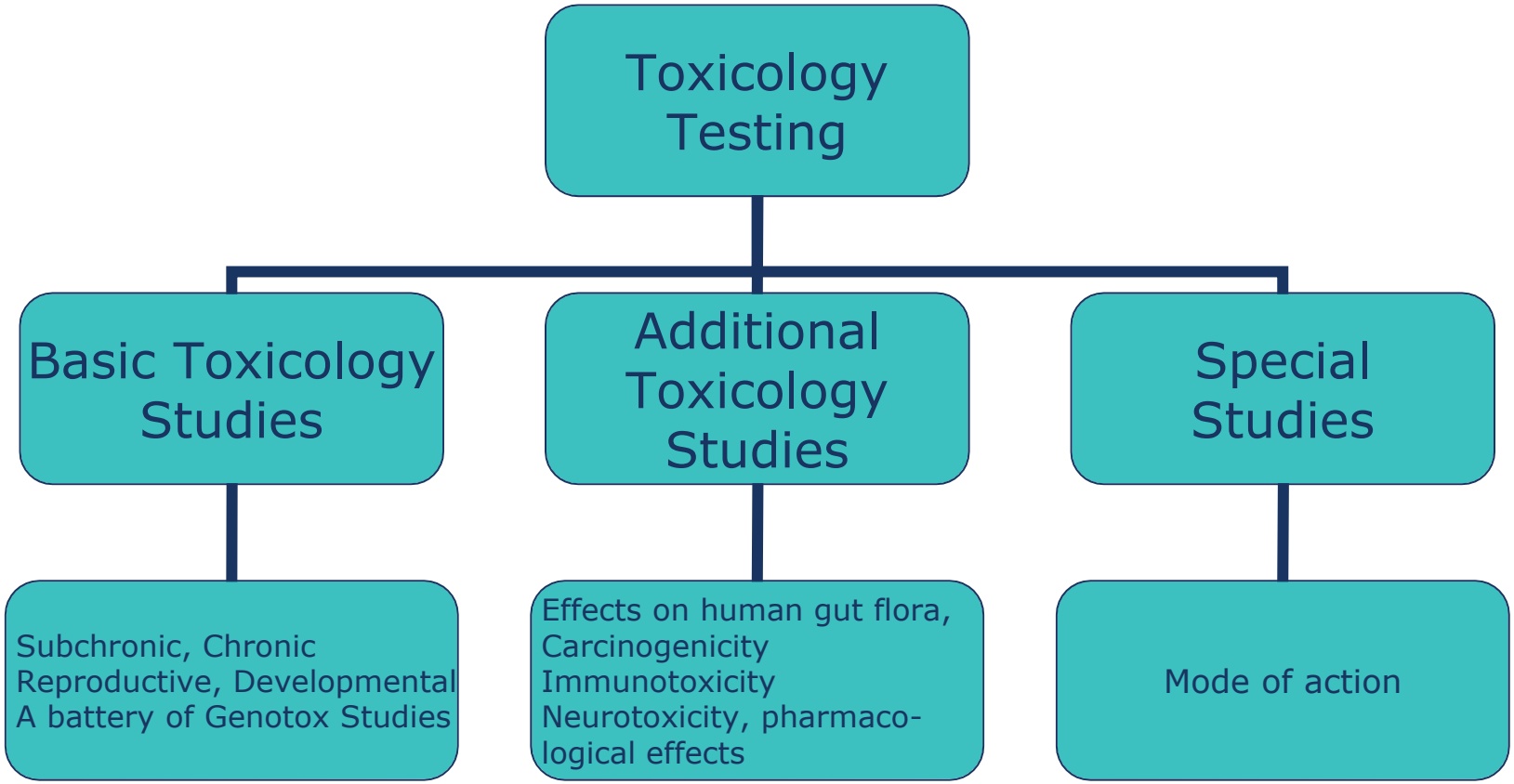
- Establish a human Acceptable Daily Intake (ADI) level for total drug residues in edible tissues based on toxicology testing
- ADI - An estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard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

# 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 | 20 g |

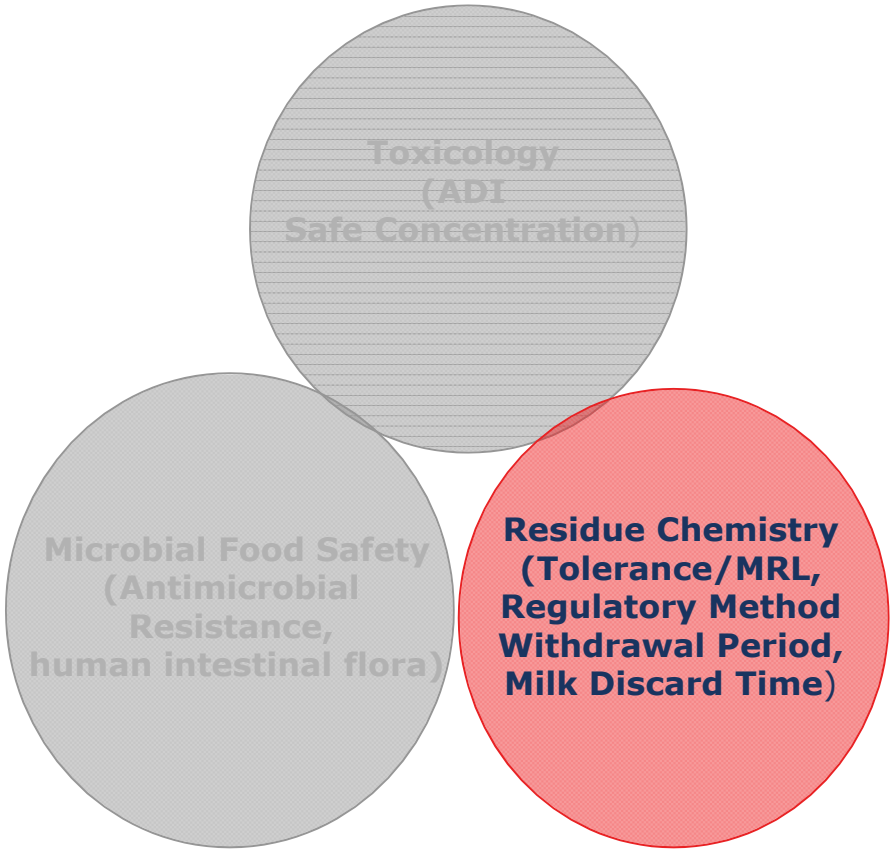
# Recommended Testing Approach



# Summary

- Toxicology human food safety assessment 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.

# Human Food Safety Assessment



# Objective of Residue Chemistry Studies

- Mitigate the hazard identified in the toxicology or microbial food safety studies by controlling exposure with assignment of MRL and withdrawal period.

Risk = Hazard X Exposure

# Establishing MRLs
## Codex Alimentarius

- Global reference established by FAO and the WHO (Codex Alimentarius Commission)
- Collection of standards, codes of practice, guidelines and other recommendations
- Formulating and harmonizing food standards
- Legal parameters for World Trade Organization Agreements
- CCRVDF

# JECFA Joint Expert Committee on Food Additives

- First joint FAO/WHO Conference on Food Additives in 1955 led to creation of JECFA
- International expert scientific committee
- Evaluation of contaminants, naturally occurring toxicants and veterinary drugs in food
- 2600 food additives, 50 contaminants and naturally occurring toxicants and residues of approximately 95 veterinary drugs

# What does JECFA do for residues of veterinary drugs in food?

- Elaborates principles for evaluating their safety and for quantifying their risks
- Establishes ADIs and other guidance values for acute exposure
- Recommends maximum residue limits for tissues and identifies target tissues
- Determines appropriate criteria for and evaluates methods of analysis for detecting and/or quantifying residues in food

# 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

# 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

# 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

# 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.
- Calculated by using the 95$^{th}$ percentile statistical tolerance limit with 95% confidence for JECFA
- The withdrawal period will appear on the product label

# Total Residue and Metabolism Study

Definition of MARKER RESIDUE

- The parent drug or metabolite in a known relationship to the concentration of total residue in the edible tissue
  - Tilmicosin (parent)
  - 22,23-dihydroavermectin B1a (metabolite)

- Relationship between the concentrations of the marker residue and total residues is usually established at representative time points during depletion in a study using drug labeled with a radioactive isotope

U. S. EXAMPLE: Marker residue and target tissue are listed in 21 CFR 556.

# 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

# U. S. Example: Software for determining milk withdrawal time

- SAS-based program available
- FDA, CVM will share system with interested parties
- Requires full suite of SAS
- *Depletion criteria for US different from those used by most registration authorities

# 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

## 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
- iii. Include regulatory measures proportionate to the relative human health risk associated with these hazards compared with other food-associated hazards

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

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

# Violative Drug Residues

- What are violative drug residues and how are they caused?
- What are the health concerns with violative drug residues?
- Goal of monitoring program is to keep violative residues out of food supply

# Violative Residues

- Use of approved drugs but residues are above MRL's
  - Product was mis-used
  - Label directions were not followed:  incorrect dose, treatment duration, route of administration, withdrawal period
- Residues from the use of unapproved drugs

# Extralabel use

- Actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling
  - Use in species not listed on the label
  - Use for indications not listed on the label
  - Use at dosage levels, frequencies, or routes of administration other than those on the label
  - Deviation from the labeled withdrawal time based on these different uses

# Veterinary Drugs with High Public Health Concern - Critically Important Antimicrobials

- Fluoroquinolones (ELDU prohibition), third generation cephalosporins, and macrolides
  - enrofloxacin (Baytril), ceftiofur (Naxcel, Excede), tylosin (Tylan)
- Are considered ‘critically important’ to treating some human infections.
- Concern about the development of resistance to these drugs by microorganisms resulting in treatment failure in humans

# Summary

- Veterinary drugs are evaluated for human food safety using a risk assessment approach.
- MRLs are established as the legal safety limit of residues in edible tissues.
- Human food safety concerns are associated with consuming edible tissues containing violative residues.

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