

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

USDA United States Department of Agriculture
Food Safety and Inspection Service

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Science

Microbiology

Baseline Data
Data was obtained to estimate the prevalence and levels of bacteria on a sample of inspected carcasses. Studies focus on bacteria of concern to public health.

Raw Ground Beef - E. coli O157:H7 Testing Results
A description of E. coli O157:H7 testing program for raw ground beef, and links to data tables.

Ready-to-Eat Meat & Poultry Results
FSIS has conducted a regulatory program on selected meat, poultry, and egg products since 1983. Products sampled and the microbial hazards for which they are analyzed are those of public health concern. This page includes a description of listeria and salmonella test results, and links to data tables.

Related Information

National Advisory Committee on Microbiological Criteria for Foods (NACMCF)
FSIS is one of the sponsors of this committee, which provides impartial, scientific advice to federal food safety agencies.

Salmonella Testing of Raw Meat & Poultry Products, 1998-2006: Annual Progress Report | PDF
FSIS verifies that establishments are meeting performance

Science

- HACCP & Pathogen Reduction
- Laboratories & Procedures
- Data Collection & Reports
 - Microbiology
 - Chemistry
 - Pathology Projects
 - Animal Disposition Reporting System
 - FoodNet
 - Risk Assessments

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

PulseNet

The National Molecular Subtyping Network for Foodborne Disease Surveillance

FDA
U.S. Food and Drug Administration

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

USDA
U.S. Department of Agriculture

PHL
Public Health Laboratory

CSTE
National Center for State, Territorial, and Tribal Epidemiology and Prevention

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

USDA United States Department of Agriculture

Agricultural Marketing Service

Science & Technology Programs

Microbiological Data Program
Progress Update and 2006 Data Summary

United States Department of Agriculture

Agricultural Marketing Service

Science & Technology Programs

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

• safer food supply
• protect public health
• consumer confidence
• international trade

FDA
USDA
CDC

NARMS

National Antimicrobial Resistance Monitoring System
Food and Drug Administration • Centers for Disease Control and Prevention • United States Department of Agriculture

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

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CDC Department of Health and Human Services
Centers for Disease Control and Prevention

Health & Safety Topics | Publications & Products | Data & Statistics

FoodNet - Foodborne Diseases Active Surveillance Network

The Foodborne Diseases Active Surveillance Network (FoodNet) is the principal foodborne disease component of CDC's Emerging Infections Program (EIP). FoodNet is a collaborative project of the CDC, ten EIP sites, the U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA).

The project consists of active surveillance for foodborne diseases and related epidemiologic studies designed to help public health officials better understand the epidemiology of foodborne diseases in the United States.

California Colorado Connecticut Georgia Maryland Minnesota New Mexico New York Oregon Tennessee

FoodNet Vision 2007 Meeting Information [Detailed map view](#)

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

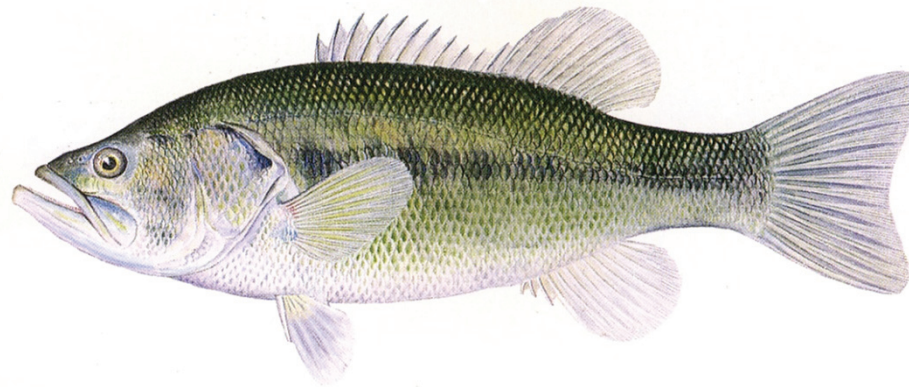
U. S. EXAMPLE: FDA Veterinary Drug Approval Process

- 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

**Center for
Veterinary Medicine**

**Office of New Animal
Drug Evaluations**

**Division of
Human Food
Safety**

**Toxicology
Team**

**Residue
Chemistry
Team**

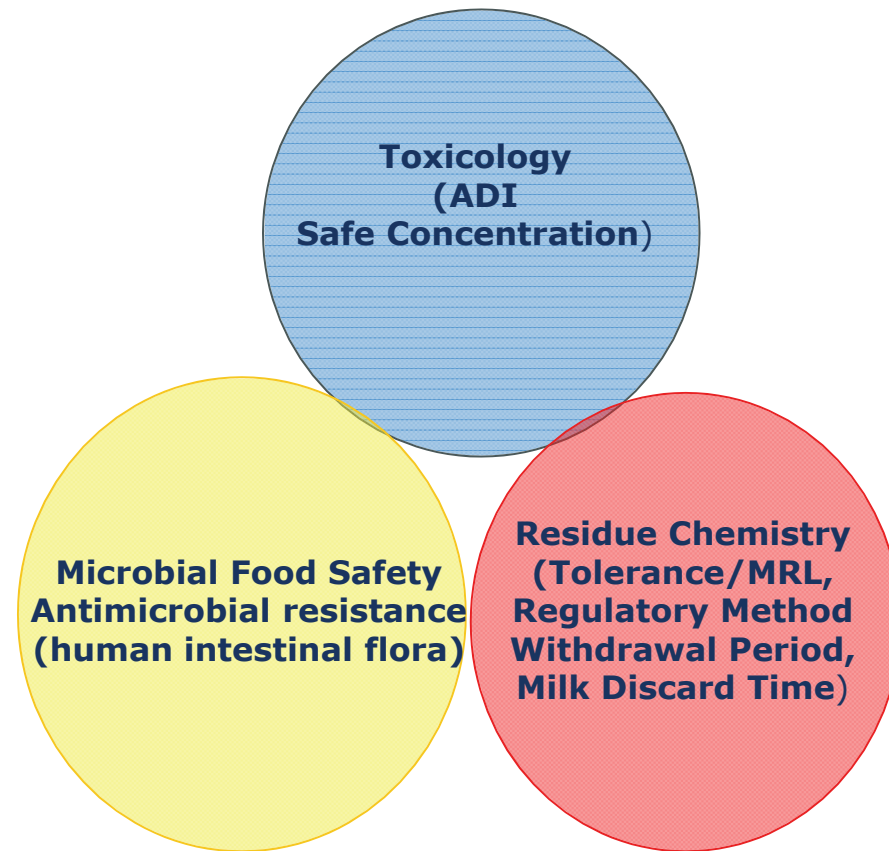
**Microbial Food
Safety Team**

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

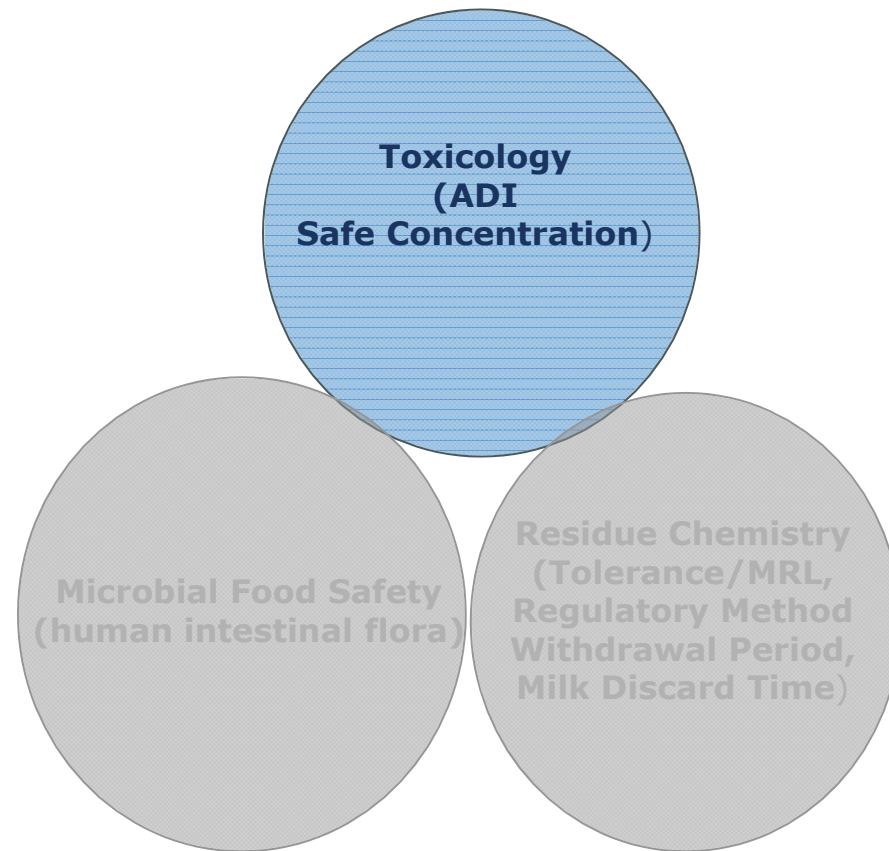
VICH Safety Guidelines Implemented as FDA/CVM Guidance for Industry (GFI)

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

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

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

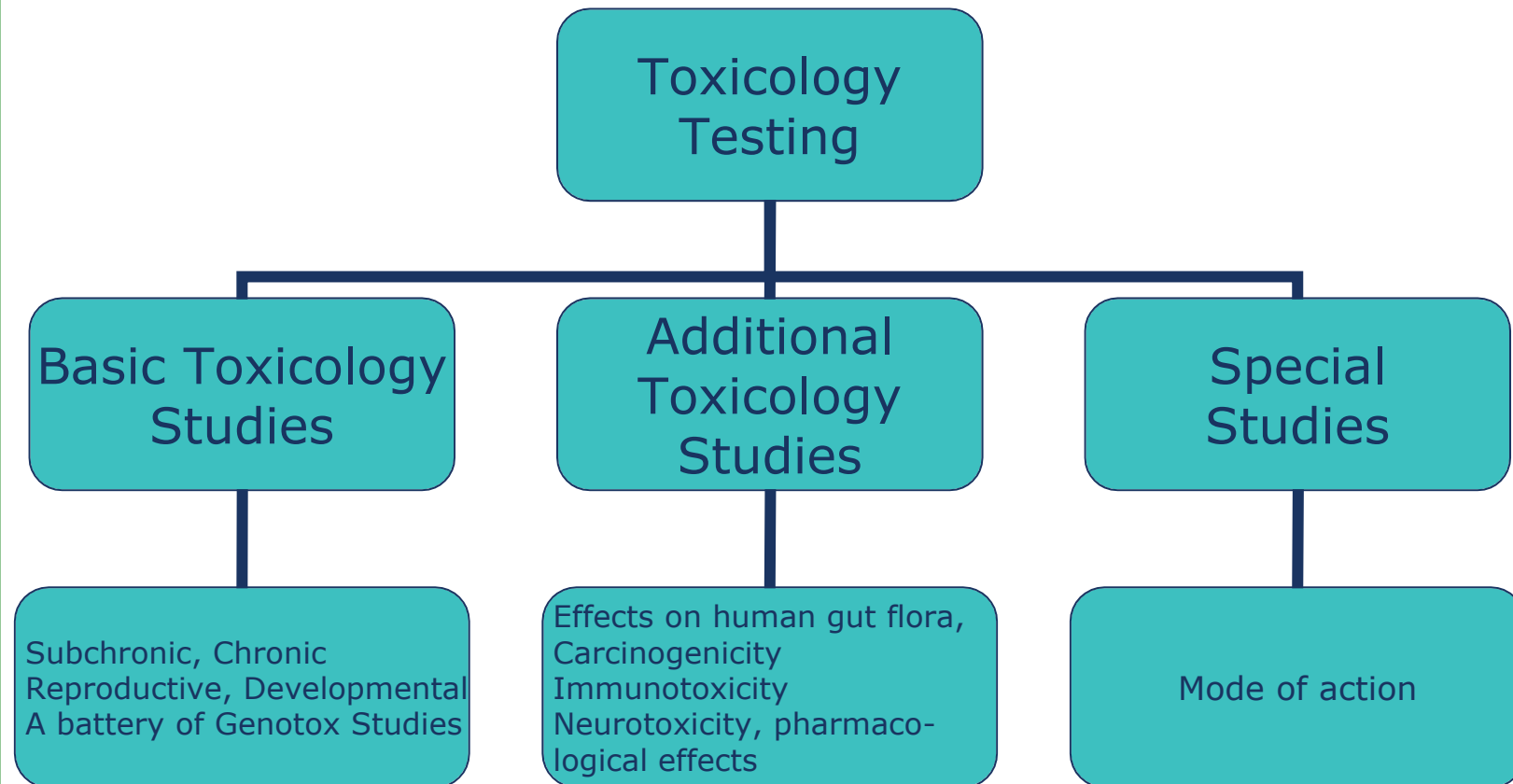
- Establish a human Acceptable Daily Intake (ADI) level for total drug residues in edible tissues based on toxicology testing
- ADI - An estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard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

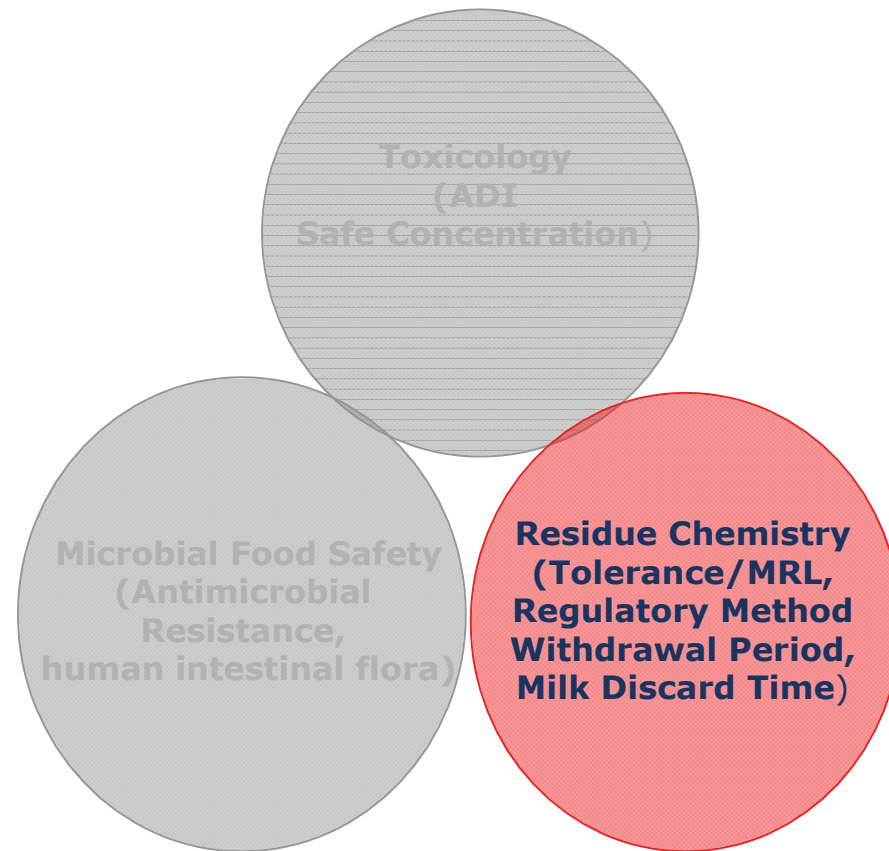
Recommended Testing Approach



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.

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

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 95th 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 production 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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