Avoiding residues and an FDA Inspection

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USDA–FSIS Residue Testing

- New approaches in 2012 – Blue Book
  - Surveillance sampling – random – 52+ analytes
    - KIS (Kidney Inhibition Swab) – more sensitive screening
      - Multi-test system vs. historic single test
      - Confirmatory tests - More specific/lower detection
    - Wider range of compounds tested – not just antibiotics
  - Inspector driven sampling – parallel to surveillance
    - Ante- or postmortem inspections create questions
    - Prior history – suspect populations
  - Purchases from known violators - pressures on plant

USDA–FSIS Residue Testing

- Compounds to be tested – plan established annually
  - many not previously tested – new and improved tests
  - risk-based selections – human health/potential sources
    - Antimicrobials – approved
    - AMDUCA prohibited/limited compounds
      - Clenbuterol and cephalosporins
    - Hormones – endogenous and exogenous (MGA)
    - Analgesics/anti-inflammatory drugs – flunixin, others
    - Herbicides/pesticides
    - Carbadox, arsenicals and other chemotherapeutics
    - Anti-parasiticides
    - Heavy metals – lead and cadmium, dioxins

USDA–FSIS Residue Testing

- Effects from FSIS changes
  - Increased residues testing = found and reported
    - Lower/more specific detection levels – penicillin!!!
    - New compounds found –previously unknowns – Flunixin!!
- HACCP - non-compliance for plant - extreme = shuttered
  - Pressures on packers to solve "problem"
    - Shift blame – producer/buying station
    - Increased interest in standard ID to production site
    - FSIS Repeat Violator List consulted
  - Pressures on producers – reduce risks = change practices
    - Market access
    - FDA inspections

FSIS RESIDUE VIOLATION INFORMATION SYSTEM

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WEEKLY RESIDUE REPEAT VIOLATOR FOR USE BY FSIS INSPECTION PROGRAM PERSONNEL

Part I: This part is intended to assist Inspection Program Personnel to identify producers with more than one residue violation in the last 12 months either in the same establishment or different establishments.

Source Name By State	Plant Name / ID	Sample ID / Date Collected / Tags	Tissue	Residue	-----(ppm)----- Value	Tolerance
FARMER JOHNS SOWS P O BOX 398 TAYLOR,AZ 85939-0398	OLDHAMS LLC 619 EAST 4TH STREET HOLTON, KS 05536 M	100367397 01/16/13 SOWS BACK TAGS 47MH9685 BACK TAGSNONE	LIVER KIDNEY	FLUNIXIN PENICILLIN	0.0102 DETECTED	0 0
		100361679 01/09/13 SOWS BACK TAGS 47MH8927 BACK TAGSNONE	KIDNEY	PENICILLIN	DETECTED	0

KIS screening test – plant level

Table 1. KIS™ and FAST Specific Test Technology-Claimed Detection Limit in Kidney and US tolerances in Bovine and Porcine Kidney				
Antibiotic Drug	KIS™ Test Detection Level (ppb)	FAST Detection Level (ppb)	US Tolerance Bovine Kidney (ppb)	US Tolerance Porcine Kidney (ppb)
Penicillin G	30	800	50	zero
Ampicillin	100	400	10	10
Amoxicillin	100	400	10	N/A
Cloxacillin	300	4000	10	N/A
Ceftiofur	4000	400	400	250
Cephapirin	100	360	100	N/A
Sulfamethazine	500	20000	100	100
Sulfadimethoxine	250	4000	100	N/A
Sulfathiazole	250	8000	N/A	100
Oxytetracycline	3000	1200	12000*	12000*
Chlortetracycline	12000	800	12000*	12000*
Tetracycline	1000	1200	12000*	12000*
Tylosin	400	24000	200	200
Erythromycin	500	24000	100	100
Pirlimycin	1000	8000	N/A	N/A
Tilmicosin	2500	N/A	N/A	N/A
Tulathromycin	400	N/A	N/A	15000
Neomycin	4000	400	7200	7200
Gentamicin	750	160	N/A	400
Streptomycin	10000	1200	2000	2000
Dihydrostreptomycin	2000	1200	2000	2000
Florfenicol	10000	8000	N/A	N/A
Chloramphenicol	50000	16000	N/A	N/A
Enrofloxacin	25000	1600	N/A	N/A
Ciprofloxacin	25000	1200	N/A	N/A
Spectinomycin	10000	80000	4000	N/A
Novobiocin	5000	4000	1000	N/A
Trimethoprim	1000	12000	N/A	N/A
Virginiamycin	25000	4000	N/A	400
Bacitracin	10000	N/A	500	500

USDA-FSIS Residue testing

- Testing as result of KIS+ in plant
  - 7 – plate bioassay – run on all samples after KIS+
    - tetracyclines – chlortet, oxytet, tetracyline HCL
    - Aminoglycosides - streptomycin, gentamycin, neomycin,
    - Macrolides – Tilmicosin, tulathromycin, tylosin etc.
    - Beta-lactams – Pen G –bioassay to 25 -30 ppb
    - Fluoroquinolones
    - Cephalosporins – Naxcel, Excede
  - AMDUCA prohibited products
- Most bioassays backed by liquid chrom/Mass spec

Drugs Prohibited - *Extralabel Use in Food Animals*

(Check for updates on the FDA web site at www.fda.gov/cvm)

- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol (DES)
- Dimetridazole
- Ipronidazole
- Other Nitroimidazoles
- Furazolidone, Nitrofurazone, Other Nitrofurans
- Sulfonamide drugs in lactating dairy cows (except approved use of sulfadimethoxine,sulfabromomethazine, and sulfaethoxypyridazine)
- Fluoroquinolones – all forms
- Glycopeptides (example: vancomycin)
- Phenylbutazone in female dairy cattle 20 months of age or older
- Adamantane and neuraminidase inhibitor classes of drugs that are approved for treating or preventing influenza A are prohibited therapy in chickens, turkeys, and ducks (Effective: June 20, 2006)

Cephalosporin limitations to ELDU

Limitations

In food animals - only use according to label
Use not approved in that species = human products
Not for use for disease prevention activities

Exceptions:

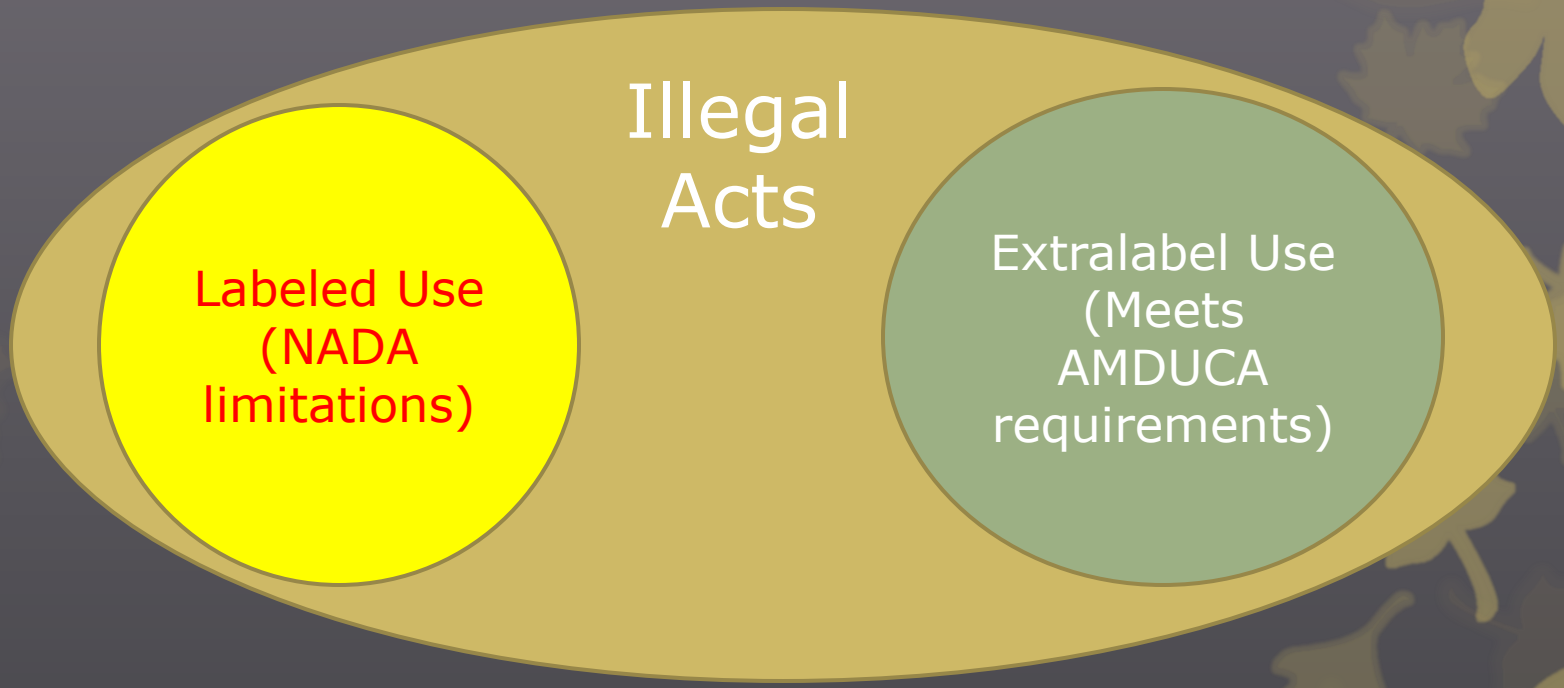
Extra label use of cephapirin in food-producing animals;

Used to treat or control an extra label disease indication, as long as this use adheres to a labeled dosage regimen
- dose, route, frequency, and duration of administration
- approved for that particular species/production class;
- extra label use in food-producing minor species, such as sheep, goats, etc.

Compounding – 21 CFR 530.13 and CPG 608.400

- CVM expects this to be a rare event
- Must conform to state Pharmacy requirements
- All ELDU/labeled products judged ineffective
- CVM accepts toxicant mitigation or "pig-side" apps.
- Considered "manufacturing" as default
  - Quantities produced – limited
  - Prepared in anticipation of use - limited
  - Advertising or third party sales - not
  - Circumvention of drug approval process – not
  - For food animals – not similar to approved product
- **Justification** - prevention of pain, suffering or death – *not convenience or cost*

Animal Drug Classifications



Penicillin residues – A Lesson?

- Prior to 2012 – Penicillin residues
  - Unidentified Microbial Inhibitor on screen test
  - Level of detection - ppm
  - No regulatory action
- 2012 – test modified for beta-lactams
  - Identified as Penicillin
  - level of detection – 20-30 ppb on KIS
  - Regulatory actions increased

Penicillin residues – A problem

- Most penicillin used at off-label dosages
- Injection quantities influence residue potential
  - More than 10 cc. site increases time to absorb
  - Residual left in pocket in muscle
  - Properly administered – muscle residue gone in 15 days
- Kidney is FDA target tissue for residue
  - Depletion is prolonged – 50+ days at detection levels
  - No tolerance level set in pork (50ppb in beef)

FDA Inspections

- Random – rare at practice or farm level??
- For cause inspections
  - **illegal residue violation**
  - prior delivery of bulk or prohibited drugs
  - illegal product use
  - high visibility – controversial presence in community
- Authority for inspections at production sites
  - FD+C Act – section 704
    - inspection of processing, holding or transport of food
    - livestock production – MOU - Federal Meat Inspection Act

Producer Investigations

- Medication records – probable first stop – PQA Plus GPP #
  - Adequacy of records – information captured and retained
  - Adherence to withdrawal time requirements
  - Animal ID practices
- Examination of all drugs on the premises
  - Injectable and water medications
  - Medicated feeds – complete and premixes
- Examination of drug storage
  - Adequacy of storage and inventory – labels and products
  - Access – who is responsible – maintenance of records etc.
- Employee Interviews – may occur during tour
  - Responsible for drug usage/administration
  - Training and understanding of training
  - Evaluate proficiency ??
- Records for animals in interstate commerce ??

FDA Inspections

- Strategies to survive/succeed
  - Be courteous and professional
  - Be sincere and respectful of time
  - Be truthful – answer only question asked
  - If unclear about question – ask for clarity
  - Don’t offer additional information or explanations
  - During site visit – be aware of areas of interest
  - Remember inspector has a public health mandate
    - sniff of “evasion/wrongdoing” = more inspection
    - looking for reasons or causes for public health injury

FDA Inspections

- Producer rights/expectations
  - Allow copies of originals
  - Duplicate samples of any taken by inspector
  - Maintain records of all materials taken
  - If offered, read inspector's report/notes
  - If questions – attempt to clarify in notes (not verbal)
  - Don't sign unless fully agree
  - Signature indicates facts as presented are acceptable
- REMAIN COLLECTED AND PROFESSIONAL

Questions??