The Future of Antimicrobials

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Future of Antimicrobials

- **Disclaimer** - My “CRYSTAL BALL” is cracked !!!
- What’s trending – restrictions to animal agriculture??
  - Limitations to labeled usages
  - Prescription controls for OTC products
  - Constriction of Extra-label use –
    - Direct - Limit to approved uses
    - Indirect - Residue detection reduce choices
  - Residue detection/violative residue actions
Animal Drug Classifications

Same drug – different outcomes

Labeled Use (NADA limitations)

Illegal Acts

Extra-label Use (Meets AMDUCA requirements)
Cephalosporin Limitations

- Limits use in food animals – April 5, 2012
  - unapproved dosages, frequency, route of admin.
  - products not approved in that species
  - use solely for disease prevention

- Exemptions to these limitations
  - Treat/control disease at labeled dosages for that class of livestock – change target organism
  - minor use species not limited – sheep, rabbits
Figure 1. Glycopeptide resistance trend in *E. faecium* from Danish pigs, pork and healthy humans (Danmap 2006, 2007).
Guidance - 209

- **Purpose**
  - Outline FDA public health concerns
  - Summarize key scientific reports
  - Outline recommendations for “judicious” use in food-producing animals

- **What is it??**
  - **NOT** legally binding recommendations
  - Discussion document – indicates future actions
  - Recommendations apply to food-producing animals
Guidance - 209

Terms to remember

- medically important drugs = drugs important as therapeutics in humans
- Judicious use = used for treatment, control and prevention of animal diseases under rules
- Injudicious use = all other animal drug usages
- Therapeutic drugs – used to treat specific diseases
- Subtherapeutic = low level animal drugs used for growth promotion and feed efficiency
Guidance 209

- **Principles for guidance – food producing animals**
  - medically important drugs should be limited to uses necessary for assuring animal health
  - use should include veterinary oversight

- **Factors for prevention use – approval**
  - evidence of drug effectiveness
  - use consistent with accepted veterinary practices
  - use linked to specific etiologic agent
  - use appropriately targeted
  - no reasonable alternatives
Draft Guideline - 213

- Designed to implement GFI 209
  - **Voluntary** phase-in over 3 years
    - Remove OTC status on water and feed (injectables?)
      - Water – Script for use
      - Feed – Veterinary Feed Directive
  - New label indications/Claims
    - Directed at specific disease
    - New concentration must be proven stable, residue information and meet GFI #152 for resistance – essentially require short-term treatment only if “medically important” drug
  - **Bottom line** – no new dosages or indications
Supplemental activities

• **Guidance #152**
  ◦ risk-based approval testing process for NADA
  ◦ applies to food-animal uses primarily
  ◦ makes use other than targeted to small groups or individual treatment difficult

• **PAMTA – Preservation of Antibiotics for Medical Treatment Act – HR 695**
  ◦ phase out of non-therapeutic use of medically important antibiotics in farm animals
  ◦ currently stalled; is back and bi-partisan????
Antimicrobial Resistance History

- Not new USA issue – FDA proposed subtherapeutic Pen/tetracycline ban in 1977 – Congress squelched
- Sweden bans all growth promotants - 1986
- Avoparcin ban in 1995-1997 in EU
- Danish “voluntary” growth promotants ban -2000
- EU growth promotant ban – 2005
- Danish ban of cephalosporin use – 2010
- Danish “Yellow Card” system
Danish Antimicrobial Use – Total

Figure 4.1. Consumption of antimicrobial agents and growth promoters in animal production, number of pigs produced and prescribed antibacterials in humans, Denmark

DANMAP 2011
Figure 1. The Yellow Card Initiative in short
Antimicrobial use pressures - Danish

Yellow card – exceed threshold in 9 month

- three age groups for pigs to meet
  - nursery pigs – weaning to 30 kg. - 28 ADD/100 pigs/day
  - grower pigs – 8 ADD/100 pigs/day
  - Sows, gilts, boars – 5.2 ADD/100 pigs/day
- must not keep drugs at holding for feed and water inclusion after first use
- veterinarians must limit prescription length
- unannounced visits by Dan. Veterinary Feed Authority
- goal – stay below the threshold
Antimicrobial use pressures - Dutch

- Centralized data collection – 2011
  - VetCIS – centralized data for drug use by veterinarians and producers – similar to Vetstat
  - IKB (nat. quality progr.) records from producers
  - Pharma houses report annually – FIDIN
  - used to estimate antimicrobial usages

- LEI program – research program??
  - stratified survey of farms for usage patterns
  - conducted annually
Antimicrobial use pressures - Dutch

- Goal – 20% - 50% reduced antimicrobial use
  - benchmark year – 2009
  - 2011 – 20% goal - 32% reduction achieved
  - 2015 - ??
- Dutch - less central controls than Danes
- Appealed to national pride
- Minimized FQs and cephalosporins in animals
- Restricted ads for antimicrobial use
Total sales in the Netherlands (gram per kg; FIDIN)
Sales patterns NL & other countries

Report 'Trends in the sales (…) in nine European countries'
Total sales NL and other countries

Note the differences in the scales.
Antimicrobial use pressures - EU

- Germany - central reporting system in 2012
  - have goal to reduce animal drug use
  - mechanisms are being developed
- European Medicines Authority (EMA)
  - establish standardized national systems for drug use data collection
  - considerable variations – none close to Vetstat
  - work in progress -
Increased drug use reporting - USA

- 2008 – Animal Drug User Fee Amendments
  - required pharma to report drug sales annually
  - no separation by product type or species
  - currently FDA looking for ways to improve data

- 2012 – Waxman offering more detailed
  - applies only to food animals
  - only products that are important for human use
  - require feed mills to report use in feeds
FSIS initiative in Residue Prevention

- Increase testing across all species
- Multiple analyses on each sample
- Multi-plex tests to give multiple results
- Analyses 52+ chemicals vs. per sample
- New lower detection limits
- Processor responsible as part of HACCP
- Violations are given to FDA for farm inspections
Compounds in 2010 NRP

- Antibiotics (bioassay)
  - Flunixin
  - Lead and Cadmium
  - Nitrofurans
  - Nitroimidazoles
  - Sulfonamides
  - Thyreostats
  - Trenbolone
  - Zeranol

- Arsenic
- Avermectins
- Beta Agonists
- Carbadox
- Chloramphenicol
- CHC/COP
- Florfenicol
Kidney Inhibition Swab (KIS™) Test

- Antibiotic Detection Test for Fresh or Thawed Kidney Tissue

- Principle of Detection is Microbial Inhibition
  - Test remains blue/purple in presence of antibiotic
KIS™ Test Results

- Yellow or yellow/green colors are **negative**.

- Blue/purple colors are **positive**.

- Yellow or yellow/green in lower half of vial with blue/purple or brown in upper half of vial are **CAUTION**. These samples should be interpreted as **negative**.
FSIS – New testing

<table>
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<tr>
<th>Antibiotic Drug</th>
<th>KIS™ Test Detection Level (ppb)</th>
<th>FAST Detection Level (ppb)</th>
<th>US Tolerance Bovine Kidney (ppb)</th>
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Inspector Generated Samples: Swine

2005-2010 Number of Samples under Inspector Generated Sampling Program
Animal Class (Swine)

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<tr>
<th>Year</th>
<th>Boars/Stags</th>
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<td>2007</td>
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<td>2010</td>
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</table>

2010 NRP Data
Preliminary
FSIS Enforcement

Identification of an Establishment Purchasing Animals with Violations from Same Source Suppliers, the District Office:

- Notify the Inspector in Charge (IIC) and the Front-line Supervisor (FLS) at that establishment

- Notify the IIC of any known violations at other plants by this same source supplier

- Instruct the PHVs to advise the establishments of this development
Residue Violators Alert List

- List of individuals or firms responsible for repeated drug, pesticide, or other chemical residue violations in animals presented for slaughter
- Updated monthly and publicly accessible through the Regulatory Enforcement and the Science links on FSIS website

www.FSIS.USDA.GOV/Regulations&_Policies/Regulatory_Enforcement/index.asp

FDA Regulatory Investigations

- Investigators - right to examine production practices
  - Reasonable times
  - “For cause” or random??
- Pre-plan for FDA inspection – plan in place before visit
  - Designate a senior member to handle investigation
  - Alert staff of steps to take when inspector arrives
  - Learn your rights in state – contact pork producers
  - Keep records in order

Remember inspector has job to do
FDA Inspections

- Initial interview
  - purpose of inspection
  - scope of inquiry

- Expectations for inspection
  - records review of pertinent information
  - facility tour - probable
  - interview of staff – highly possible
  - “follow the trail” once started
  - takes time, patience and social skills
Producer Investigations

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
  Responsible for drug usage/administration
  Training and understanding of training
  Evaluate proficiency ??
Medication records
  Adequacy of records – information captured
  System for capturing after treatments
  Adherence to withdrawal time requirements
Records for animals in interstate commerce
Medication records

- Requirements – see PQA Plus GPP #4; CPG 7125.37
  - animals treated
  - dates of administration
  - drug administered
  - route of administration
  - amount administered
  - person who administered
  - withdrawal period
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

- 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

THANK YOU YOUR ATTENTION