# Antimicrobial and drug use in swine

Locke A. Karriker, DVM, MS, DACVPM Associate Professor and Director, Swine Medicine Education Center Iowa State University

# Background and definitions...

- US Department of Agriculture (USDA)
  - Food Safety Inspection Service
    - Tests pigs and pork for contaminants and disease
- US Food and Drug Administration (FDA)
  - Safety and efficacy of drugs entering the human food supply
  - Pigs (even pet pigs!) are defined as part of the human food supply
  - More regulations for treatment than companion animals

# Background and definitions...

- FDA approves the labels for drugs that are used in food animals
- Label specifies indication, dose, route, duration, frequency of treatment and meat withdrawal period
- Over-the-counter (OTC) drugs are approved for use by non-veterinarians without a prescription
- All others require a veterinarian's prescription

## Background and definitions...

- Extra-label-drug-use (ELDU) is use of a drug in any manner different than that specified on the label
- ELDU of OTC drugs is illegal.
- ELDU in feed is illegal.

## How Drugs are Used in Swine Production

- Primarily for treating or preventing disease
- Hormones are not used to improve growth or change body conformation
  - Very rarely used to manage reproduction in adults (not market animals)
- Sub-therapeutic uses of medically important (to humans) drugs has been voluntarily stopped and is ended by regulation in 2016.

## **Routes of Administration**

• Injection or administration to individual pigs

• Administration through the water supply

• Administration through the feed supply

## Injection or individual administration

- Generally the highest efficacy but greatest challenge in large populations with aggressive and rapidly moving disease.
- OTC (over the counter, non-prescription) options are currently available (ending in 2016)
- Extra-label use (with veterinary prescription) is allowed.

## Administration through water supply

- Generally reserved for aggressive and rapidly moving disease.
- OTC (over the counter, non-prescription) options are currently available (ending in 2016)
- Extra-label use (with veterinary prescription) is allowed.

# Administration through feed supply

- Generally reserved for prevention of known disease challenges, especially intestinal infections.
- OTC (over the counter, non-prescription) options are currently available (ending in 2016)
- Extra-label use is **NOT** allowed.

## **Regulatory Issues**

## Key Concepts That Drive the Issues

- Any chemical added to the human food supply is considered an adulterant until proven otherwise.
- Pigs (ALL PIGS) are considered human food in the U.S.
- The Food and Drug Administration (FDA) of the Department of Health and Human Services is charged with ensuring the <u>safety and efficacy</u> of human drugs and animal drugs that enter the <u>human food supply</u>.

## Key Concepts That Drive the Issues

• The pig must be free of drug and have no residues at marketing unless a tolerance for the drug is established.

 When veterinarians recommend or prescribe a drug for use, they are accountable for ensuring compliance. If scientific information on the safety of food products made from an animal treated with a human drug or an animal drug that is approved only for companion animals is not available, you must take appropriate measures to assure that the animal and its food products will not enter the human food supply.

#### What's the target?

# If there is a tolerance established by the FDA, you must be below the tolerance in the animal tissues.

If there is NOT a tolerance established by the FDA, you must ensure that there is no detectable residue.

# Where do I find out what U.S. tolerances exist?

21 CFR par 556 Tolerances for Residues of New Animal Drugs in Food

## What about other countries?

MRLS Database – requires registration

http://www.mrldatabase.com/

# Where do I find out what U.S. tolerances exist?

21 CFR par 556 Tolerances for Residues of New Animal Drugs in Food

## If no tolerance, what is detectable?

Much tougher issue.....

## "Zero' isn't what it used to be!!"

### 1 part per million = 1 microgram per milliliter

aka

### $1 \mu g / mL = 1 ppm$

~1 second in 11.6 days = 1 ppm

~1 second per 31.7 years = 1ppb (1 nanogram/mL)

# The Goal is to Keep Producers and Clients OFF of this list:

## <u>Residue Repeat Violator List for Use by FSIS</u> <u>Inspection Program Personnel</u>

http://www.fsis.usda.gov/wps/portal/fsis/topics/data-collection-andreports/chemistry/residue-chemistry



| http://www.fsis.usda.gov/wps/wcm/connect/f69f356d-0ae7-4007-b334-bca63c6703a0/Residue_IPP.pdf?M - Internet Explorer           |                 |                             |                 |   | _ B ×                                     |
|---|-----------------|-----------------------------|-----------------|---|---|
| 🔍 🗢 🥥 http://www.fsis.usda.gov/wps/wcm/connect/f69f356d-0ae7-4007-b334-bca63c6703a0/Resid 🔎 🗾 😏 ሯ Data Collection and Reports | 🥝 fsis.usda.gov | Data Collection and Reports | 🥖 fsis.usda.gov | × | 合 🛧 瑛                                     |
| e Edit Go to Favorites Help   |                 |                             |                 |   | 🗙 🍕 Convert 👻 🔂 Select                    |
| s 🎕 000000 🖨 Suggested Sites 🔹 🖨 Web Silce Gallery 🔹  |                 |                             |                 |   | 🏠 🔹 🔂 👻 📑 🖶 👻 Page 🔹 Safety 🔹 Tools 👻 🔞 👻 |
|   |                 |                             |                 |   |   |

#### FSIS RESIDUE VIOLATION INFORMATION SYSTEM

6

Done

September 03, 2015

#### 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.

|  |   | Sample ID / Date  |                  |                               | (ppm)                |           |
|--|---|---|------------------|-------------------------------|----------------------|-----------|
| Source Name By State   | Plant Name / ID   | Collected / Tags  | Tissue           | Residue                       | Value                | Tolerance |
| ANGELO VIERRA<br>931 S. BLAKER ROAD<br>TURLOCK,CA 95380-9322 | LOS BANOS ABATTOIR<br>21104 W HWY 152 LOS BANOS, CA<br>00400 M            | 101051214 03/18/15<br>COWS - DAIRY<br>BACK TAGS<br>93DM 1375              | KIDNEY           | DESFUROYLCEFTIOFUR            | 3.18                 | .4        |
|  | LRN PROCESSORS, INC.<br>130 N SANTA FE GRADE RD. NEWMAN,<br>CA<br>27300 M | 101026822 02/13/15<br>BOB VEAL<br>BACK TAGS<br>CA DG 0 125                | KIDNEY<br>KIDNEY | CIPROFLOXACIN<br>ENROFLOXACIN | DETECTED<br>DETECTED | 0         |
| AREA 51 RANCH<br>7976 AVENUE 84<br>PIXLEY,CA 93256-9518      | J J MEAT CO.<br>25699 A∨E. 5 1/2 MADERA, CA<br>04969 M                    | 101043920 03/06/15<br>BOB VEAL<br>EAR TAGS<br>13372 BACK TAGS  91 TA 7172 | KIDNEY           | SULFAMETHOXAZOLE              | DETECTED             | 0         |
|  |   | 101043927 03/06/15<br>BOB VEAL<br>EAR TAGS<br>13378 BACK TAGS  91 TA 7173 | KIDNEY           | SULFAMETHOXAZOLE              | DETECTED             | 0         |
|  |   | 101043932 03/06/15<br>BOB VEAL<br>EAR TAGS<br>13365 BACK TAGS  91 TA 7171 | KIDNEY           | SULFAMETHOXAZOLE              | DETECTED             | 0         |
|  |   | 101043949 03/06/15<br>BOB VEAL  | KIDNEY           | SULFAMETHOXAZOLE              | DETECTED             | 0         |
|  |   |   |                  |                               |                      |           |

06:10:01

# Over 125 drugs and contaminants tested for by FSIS including all drugs used in modern swine production (<15)

Aminoglycosides - antimicrobials

Arsenicals – heavy metal compounds not used in pigs but found naturally in some environments

Avermectins - parasiticides

<u>Carbadox</u> – antimicrobial

Nitrofurans - topical treatment for wounds

Analgesic/Anti-inflammatory - oxyphenylbutazone, flunixin, phenylbutazone

<u>β-Agonist</u> - salbutamol, cimaterol, ractopamine

<u>B-Lactam/Cephalosporin</u>- amoxicillin, cefazolin, desfuroylceftiofur (DCCD), ampicillin, penicillin G, oxacillin, cloxacillin, nafcillin, dicloxacillin

<u>Fluoroquinolones</u> - desethylene ciprofloxacin, norfloxacin, ciprofloxacin, danofloxacin, enrofloxacin, sarafloxacin and difloxacin;

Hormones - prednisone, melengestrol acetate, zeranol

<u>Macrolide/Lincosamide</u> - lincomycin, pirlimycin, clindamycin, gamithromycin, tilmicosin, erythromycin, tylosin, tulathromycin

Phenicol - florfenicol and chloramphenicol;

<u>Sulfonamide</u> - sulfadiazine, sulfathiazole, sulfapyridine, sulfamerazine, sulfamethizole, sulfamethazine, sulfamethoxypyridazine, sulfachloropyridazine, sulfadoxine, sulfamethoxazole, sulfaethoxypyridazine, sulfadimethoxine, sulfaquinoxaline, sulfanitran;

<u>Tetracycline</u> - oxytetracline, tetracycline, chlortetracycline

General Drugs - 2-quinoxaline carboxylic acid (2-QCA; carbadox metabolite)

Pesticides – numerous products and ingredients

# Antibiotic Resistance and Escape from the Farm

- Resistance to antimicrobials occurs naturally
  - Existed in bacteria before the first drug (penicillin) was ever used
- Treating a population of bacteria results in death of susceptible bacteria and survival of resistant bacteria
  - Therefore, higher percentage of resistant bacteria
     *after* treatment *but* resistance may have already
     been in the population *before* treatment

## Complex Pathway Between Treatment on Farm and Treatment Failure in a Human

Journal of Food Protection, Vol. 67, No. 5, 2004, Pages 980–992 Copyright ©, International Association for Food Protection

#### Public Health Consequences of Macrolide Use in Food Animals: A Deterministic Risk Assessment<sup>†</sup>

#### H. SCOTT HURD,<sup>1</sup>\* STEPHANIE DOORES,<sup>2</sup> DERMOT HAYES,<sup>3</sup> ALAN MATHEW,<sup>4</sup> JOHN MAURER,<sup>5</sup> PETER SILLEY,<sup>6</sup> RANDALL S. SINGER,<sup>7</sup> AND RONALD N. JONES<sup>8</sup>

<sup>1</sup>Hurd-Health Consulting, Roland, Iowa 50236, USA; <sup>2</sup>Pennsylvania State University, University Park, Pennsylvania, USA; <sup>3</sup>Iowa State University, Ames, Iowa, USA; <sup>4</sup>University of Tennessee, Knoxville, Tennessee, USA; <sup>5</sup>University of Georgia, Athens, Georgia, USA; <sup>6</sup>MB Consult Limited, Bingley, West Yorkshire, UK; <sup>7</sup>University of Minnesota, St. Paul, Minnesota, USA; and <sup>8</sup>The JONES Group/JMI Laboratories, North Liberty, Iowa, USA

MS 03-374: Received 21 August 2003/Accepted 4 January 2004

J. Food Prot., Vol. 67, No. 5



**Release Assessment**: Describes the probability that factors related to the antimicrobial use in animals will result in the emergence of resistant bacteria or resistance determinates (RzD).

**Exposure Assessment**: Describes the likelihood of human exposure to the RzD through particular exposure pathways.

**Consequence Assessment**: Describes the relationship between specified exposures to the RzD (the hazardous agent) and the consequences of those exposures (CVM-defined hazard)

|  | Poultry               |                         | Swine                 |                         | Beef cattle           |                         |
|--|-----------------------|-------------------------|-----------------------|-------------------------|-----------------------|-------------------------|
| Components/binomial events   | Campylobacter<br>spp. | Enterococcus<br>faecium | Campylobacter<br>spp. | Enterococcus<br>faecium | Campylobacter<br>spp. | Enterococcus<br>faecium |
| Release  |                       |                         |                       |                         |                       |                         |
| 1. Animals exposed to tylosin and tilmicosin (millions) <sup><math>a</math></sup>  | 634.2                 | 634.2                   | 49.0                  | 49.0                    | 16.1                  | 16.1                    |
| 2. Probability that RzD develops in exposed animals as a function of <sup>b</sup> :  | 1%                    | 70%                     | 2%                    | 86%                     | 1%                    | 89%                     |
| a) Bacteria present in animals   | 50%                   | 100%                    | 80%                   | 100%                    | 50%                   | 100%                    |
| b) Susceptible bacteria in population  | 90%                   | 70%                     | 95%                   | 86%                     | 99%                   | 89%                     |
| c) Resistance in human isolates  | 3%                    | 100%                    | 3%                    | 100%                    | 3%                    | 100%                    |
| 3. Probability that RzD escapes from farm <sup>c</sup>   | 100%                  | 100%                    | 100%                  | 100%                    | 100%                  | 100%                    |
| Exposure   |                       |                         |                       |                         |                       |                         |
| <ol> <li>Probability that bacteria with RzD remain on carcass after<br/>slaughter<sup>d</sup></li> </ol>   | 88%                   | 100%                    | 32%                   | 31%                     | 4%                    | 8%                      |
| Exposure and consequence   |                       |                         |                       |                         |                       |                         |
| 5.–7. Ratio ( $\beta$ ) that contaminated serving leads to human illness <sup>e</sup>  | $8.6 	imes 10^{-6}$   | $8.6 	imes 10^{-6}$     | $8.6 	imes 10^{-6}$   | $8.6 \times 10^{-6}$    | $8.6 \times 10^{-6}$  | $8.6 	imes 10^{-6}$     |
| Consequence  |                       |                         |                       |                         |                       |                         |
| <ol> <li>Probability of cases of diarrhea treated with a macrolide<sup>f</sup></li> <li>Probability that treatment fails if infection by bacteria with RzD is</li> </ol> | 3%                    | 0.0001%                 | 3%                    | 0.0001%                 | 3%                    | 0.0001%                 |
| treated with a macrolide <sup>g</sup>  | 50%                   | 100%                    | 50%                   | 100%                    | 50%                   | 100%                    |
| Risk   |                       |                         |                       |                         |                       |                         |
| Annual probability of adverse health events in the United States due to treatment of RzD-caused foodborne infection with a macrolide <sup>h</sup>                        | <1 in 14 million      | <1 in 3 billion         | <1 in 53 million      | <1 in 21 billion        | <1 in 236 million     | <1 in 29 billior        |

# What's the risk with manure?

- Environmental regulations in many states prohibit application of manure to fields when crops are present
  - So, most direct route is a carcass with manure on it (see previous discussion)
- Both antimicrobials and bacteria are present in manure
- The fate of antimicrobials relevant to swine production is poorly understood but dilution would be a significant protective factor
- The fate of bacteria that are potential human pathogens is poorly understood but substantial environmental challenges to survival are present

## What is the Environmental Impact?

- Significant deficits in research.
- Impact of antimicrobials depends on exposure to *adequate concentration* to have an effect.
- The adequate concentration is not known for many wild life species that might be exposed.
- Generally, antimicrobials are naturally occurring substances OR have relatively poor stability and break down quickly.

## How Complex is the Issue?

- Soil NOT treated with antimicrobials nor manure has bacteria with resistance factors
- Soil treated with antibiotic free manure has an increase in resistance bacteria post application
- Soil treated with manure from antibiotic treated animals has an increase in resistant bacteria post application
- Soil treated with manure from antibiotic treated animals has an increase in antimicrobials post application

## How Complex is the Issue?

- What is the route from the soil to humans when the crop is not present?
- What level of drug matters?
- How long does drug/bacteria last in the soil?

## **Additional Considerations**

Animal Welfare and Judicious Antimicrobial Use and Human Health *are not separate issues:* 

- Antimicrobial use increases animal welfare
- Antimicrobial use can reduce lesions that cause carcass contamination by bacteria during pork processing
- Antimicrobial use can increase antimicrobial resistance

## Are "Pet" Pigs considered differently by the FDA?

Food-producing species are generally considered to be animals that are 'food' regardless of where they live. These are raised or harvested and they (or food products from them) often are marketed for human consumption. One way to consider this is that this is food you can find in the grocery store or a restaurant. This includes animals like cattle, <u>pigs</u>, chickens, turkeys, deer, sheep, goats, catfish, salmon, ostriches, rabbits, pheasants, bison, bees (honey), etc. <u>Even if they are pets, in the</u> <u>laboratory, zoo, or public aquarium, these are members of food-</u> <u>producing species and they are regulated as food</u>.

Many species of animals are considered to be food-producing animals and human food safety review is required prior to approval of a new animal drug for use in that species. <u>These are also the species for which</u> <u>the drugs on the prohibited list could not be used in an extra-label</u> <u>manner.</u>

> Personal Communication, Carmela G. Stamper DVM, Office of the Director FDA Center for Veterinary Medicine, 3/13/2014

# Locke Karriker, DVM, MS, DACVPM karriker@iastate.edu

## 515-294-2283