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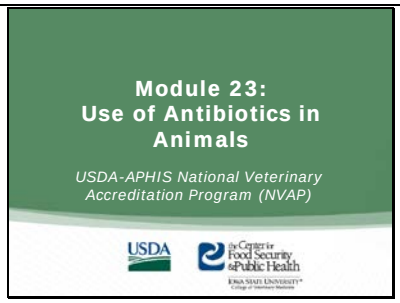

Welcome to **Module 23: Use of Antibiotics in Animals.** This module was developed as supplemental training for the USDA-APHIS National Veterinary Accreditation Program (NVAP) by the Center for Food Security and Public Health at the College of Veterinary Medicine, Iowa State University. The content for this module was finalized in February 2017 and revised in October 2017.

Presenters: As designed, slide completion time ranges from 30 to 90 seconds each, such that the entire presentation can be completed in 60 minutes.

It is strongly suggested you review the PDF or web version of this module as you are reviewing this PowerPoint prior to your presentation.

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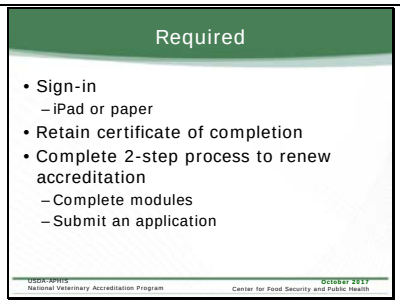

A few important points about the renewal process, first you must sign in to get credit for taking each APHIS Approved Supplemental Training Module. This will either be done using a paper sign in sheet that is being passed around or the iPad that is being passed around. Second, at the end of the presentation you will receive a certificate of completion, this is your proof you have completed the module. Please retain this for your records. Do not send it to APHIS as part of the renewal. You must submit an application for renewal as part of the two-step renewal process. This can either be done on-line or via paper. Both processes are described on the NVAP website.

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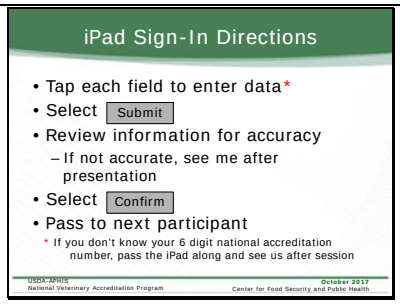

In order for the key pad to display, the participants must first tap the first field on the screen (first name field). This will display the key pad. The participant must then either tap the stylus pen or their finger into each subsequent field on the screen. The user must tap into each field. Enter your entire National Accreditation number including leading 0's.

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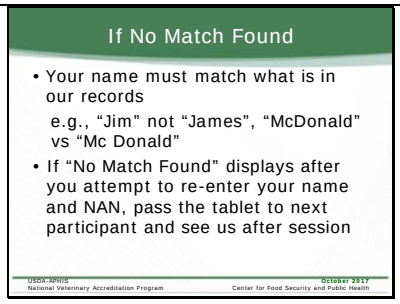

However, if they have not entered the data the way it is entered into our database they will get a No Match Found message. They should attempt to re-enter the data two more times and then pass the tablet to the next participant. They must see the instructor after the presentation to ensure they do get credit for the module they have taken. Certain reasons their name is not displayed include: Their name is not entered correctly—James vs Jim, McDonald vs Mcdonald, vs Mc Donald, etc.

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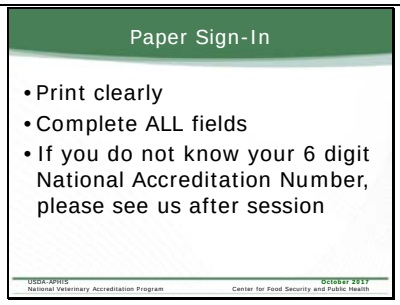

If a paper sign in is being used please make sure you print clearly or you may not get credit for the AAST module. It is critical that we have your updated email address to ensure you receive notifications from NVAP. If you do not know your six digit National Accreditation Number (NAN), please see the instructor after the presentation.

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Presenters: Please make sure your audience understands the intent of this information by reading what is written here. This informational presentation is intended to familiarize accredited veterinarians with animal health regulatory concepts and activities. Information presented here does not supersede the regulations. For the most up-to-date regulations and standards, please refer to the Code of Federal Regulations or your local VS District Office.

Slide 7

All modules are available on our website free of charge. If you want additional information about any of the presentations, you may check them out on our website where additional resources are available. The NVAP website is available by typing NVAP into your preferred search engine.

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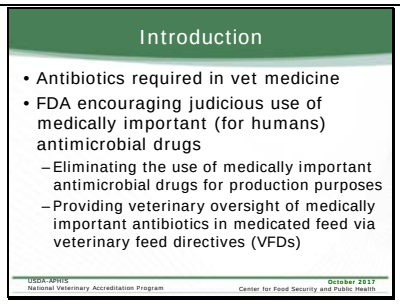

- Veterinarians diagnose, treat, control, and prevent diseases in animals
- Antibiotic treatment required to prevent animal suffering

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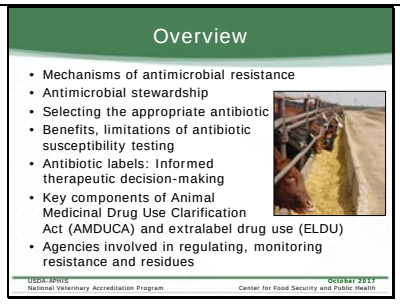

This presentation will help you:

- describe mechanisms of antimicrobial resistance in general terms;
- define antimicrobial stewardship;
- evaluate key factors for selecting an appropriate antibiotic;
- describe the benefits and limitations of various antibiotic susceptibility testing options;
- locate and interpret antibiotic labels for the purposes of informed therapeutic decision-making;
- apply the key components of the Animal Medicinal Drug Use Clarification Act (AMDUCA) to making decisions about antibiotics; and
- list the agencies involved in regulating antibiotics and monitoring antibiotic resistance and residues.

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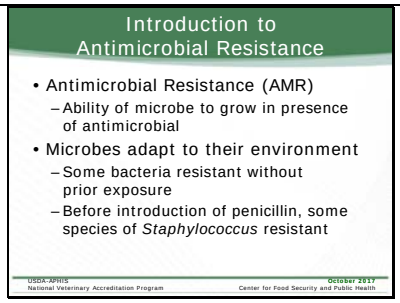

- Microbes constantly adapt to resist the antimicrobials developed to treat them
- Some bacteria are resistant to particular antibiotics or classes of antibiotics without prior exposure to the antibiotic
- Even before the introduction of antibiotics in human medicine, certain species of *Staphylococcus* expressed resistance to penicillin

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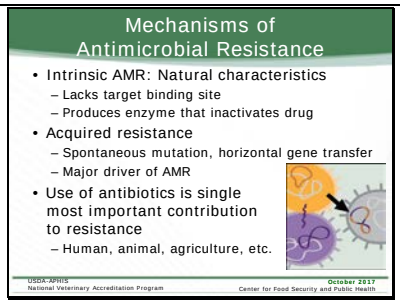

- Intrinsic AMR: bacteria naturally have structural or functional characteristics that resist activity to a particular antibiotic.
  - Example: if an organism lacks target binding sites or produces an enzyme that inactivates the drug, the organism is intrinsically resistant.
- Acquired resistance occurs when a particular bacterium undergoes spontaneous mutation of a gene or horizontal gene transfer.
  - Horizontal gene transfer: Movement of genetic elements between neighboring organisms on transferable genetic elements.
- The development of antibiotic resistance is not new or unexpected.
  - The use of antibiotics in any setting (human, animal, agriculture, etc.) is the single most important contribution to antibiotic resistance development.
  - Any antibiotic use creates a selection pressure that favors the survival and amplification of resistant strains.

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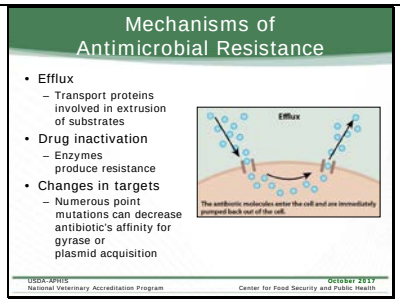

- Organisms can resist the action of antibiotics by different mechanisms
- Examples
  - Efflux pumps: Numerous bacteria have nonspecific efflux pumps, including *Mycobacterium*, *Escherichia*, and *Pseudomonas* species.
  - Drug inactivation: Many *Staphylococcus* species have developed an enzyme, penicillinase, which makes them resistant to penicillins. Cephalosporinase can produce resistance to all cephalosporins, penicillins, monobactams, and cephamycins.
  - Changes in targets: *Campylobacter* species quickly develop resistance to fluoroquinolones through point mutations.

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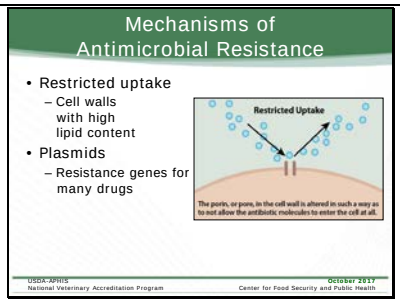

- Examples:
  - Restricted uptake: *Mycobacterium* species have cell walls that contain a high lipid content, which not only makes them resistant to killing by macrophages but also restricts uptake and penetration of antibiotic agents.
- Plasmids: Circular, self-replicating, double-stranded pieces of DNA, separate from chromosomal DNA, which can be transferred between bacteria.
  - Plasmids can contain resistance genes for many drugs; as a result, use of one antibiotic can select for resistance to multiple antibiotics.

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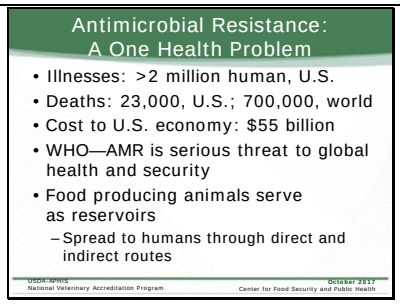

- Serious threat to One Health—humans, animals, and the environment.
- In humans, the loss of effective antibiotics undermines the ability to fight bacterial diseases and manage infections.
- CDC reported in 2013 that antibiotic resistant infections cost the U.S. economy an estimated $55 billion in direct and indirect costs (2008 dollars).
- Use of antibiotics is single most important factor leading to resistance.
- Humans may acquire resistant infections through person-to-person spread or from non-human sources, including food and animals.
  - food producing animals serve as an important reservoir for antibiotic-resistant bacteria that cause enteric infections in humans.
  - CDC estimates that in the United States, more than 400,000 of the 2 million antibiotic resistant infections are caused by *Salmonella* and *Campylobacter*, zoonotic bacteria which are transmitted commonly through food.

Sources: Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. Accessed Apr 15, 2016.
Centers for Disease Control and Prevention. Antibiotic Use in food producing Animals. Accessed May 9, 2016.
Painter JA, Hoekstra RM, Ayers T, et al. Attribution of foodborne illnesses, hospitalizations, and deaths to food commodities by using outbreak data, United States, 1998–2008. Emerg Infect Dis 2013;19(3):407–15.
Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. Accessed Dec 2016

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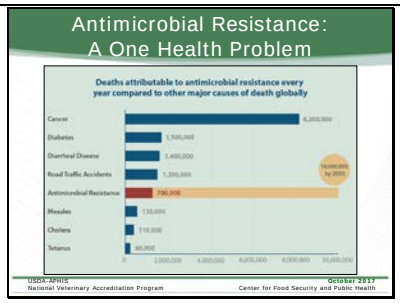

- By 2050, 10 million lives could be lost each year because of antimicrobial resistant infections
- Global cost: $100,000 trillion

Sources: Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: final report and recommendations. Accessed Dec 2016.

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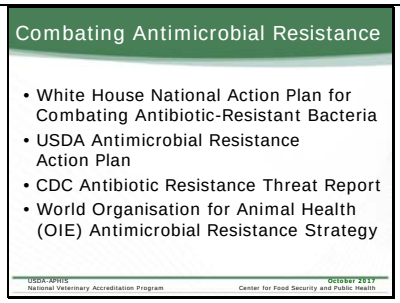

- All goals and objectives involve slowing emergence, preventing infections, improved surveillance, improved stewardship, accelerated research and development, and increased collaboration.
- As illustrated throughout this presentation, veterinarians participate in activities and are key stakeholders in achieving goals

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- Important for veterinarians to work with livestock producers and companion animal owners to avoid unnecessary or inappropriate use of antibiotics in animals.
- Antibiotic and treatment regimen only one part of a comprehensive animal or herd health plan.
  - To prevent disease, other strategies should be implemented such as appropriate husbandry and hygiene, strict biosecurity, routine health monitoring, and vaccination.
  - To control disease, management changes should be considered in addition to antibiotic use.
- Whenever antibiotics are considered, their use should be confined to cases in which treatment is likely to positively alter the disease outcome, since any antimicrobial use can result in selection for resistance.

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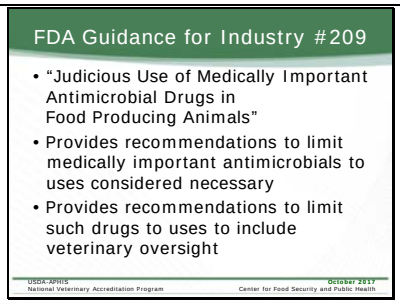

- FDA has released several guidance documents that aim to slow the emergence or spread of antimicrobial resistance by changing how medically important antimicrobial drugs can be used in food producing animals.
- Medically important antimicrobials (in human medicine) outlined in GFI #152

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FDA Guidance for Industry #213

- "New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food Producing Animals"
- Provides recommendations for drug sponsors on how to voluntarily modify use conditions
- Medically important antimicrobials
  - Medicated feed: OTC → VFD
  - Medicated water: OTC → Rx

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Federal and State Antibiotic Regulation

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Antibiotic Regulation

- Federal regulation of antibiotics
  - U.S. Food and Drug Administration's Center for Veterinary Medicine (FDA CVM)
- State regulation of antibiotics
  - State Board of Veterinary Medicine
  - State pharmacy acts
- Veterinarians must be familiar with laws and regulations

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Approved Uses of Antibiotics in Food Producing Animals

Disease Treatment	Disease Control	Disease Prevention
Animals exhibiting clinical signs	Proportion of group exhibiting clinical signs	Disease is likely to occur

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Growth Promotion and Improved Feed Efficiency

- Drugs administered to growing, healthy animals
- Production (nontherapeutic) uses (FDA, AVMA, OIE)
- FDA promoting judicious use by removing production uses of medically important antimicrobials and improving veterinary oversight (January 1, 2017) via Veterinary Feed Directive and prescription

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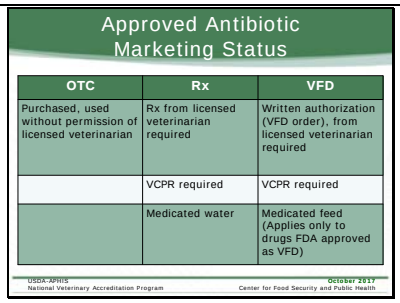

Antibiotics (and other animal drugs) are approved with one of the following marketing statuses:

- Over-the-counter (OTC)
  - Can be purchased and used without supervision or permission of a licensed veterinarian
  - Adequate directions for lay person use found on the drug label
- Veterinary prescription (Rx)
  - Prescription from a licensed veterinarian with a valid veterinarian-client-patient-relationship (VCPR) required before purchase
  - Can include drugs administered through water
- Veterinary feed directive (VFD)
  - Requires written authorization, a VFD order, from a licensed veterinarian and a valid veterinarian-client-patient-relationship (VCPR)
  - Applies only to drugs FDA approved as VFD

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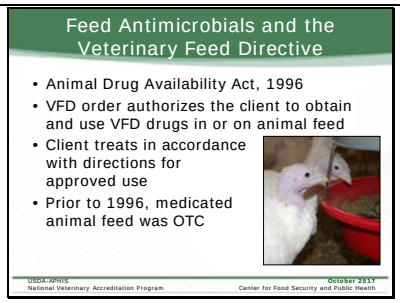

- Animal drugs dispensed in or on animal feed that require professional veterinary supervision are regulated by the FDA under the Veterinary Feed Directive (VFD).
- The VFD was established by Congress as part of the Animal Drug Availability Act of 1996 (ADAA).
  - Prior to ADAA, all medicated animal feed was dispensed over-the-counter (OTC).
- The VFD provides veterinarians the ability to authorize the client to obtain and use VFD drugs in or on animal feed.

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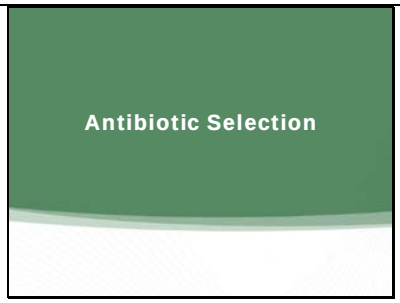

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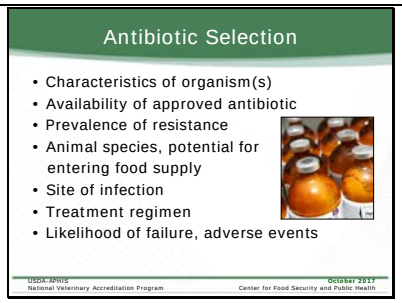

In veterinary medicine, the following key factors should be considered when choosing an antibiotic:

- Characteristics of suspected or confirmed bacterial organism(s), including antibiogram results if available;
- Availability of a species-approved and indication-approved antibiotic; and
- Prevalence of resistance in the suspected or confirmed bacterial organism(s).

Other considerations include the

- Animal species to be treated and their potential for entering the food supply;
- Ability of the antibiotic to reach the site of infection at an effective concentration;
- Treatment regimen;
- Likelihood of treatment failure; and
- Likelihood of antibiotic-associated adverse events.

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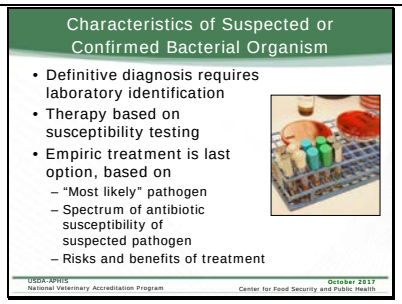

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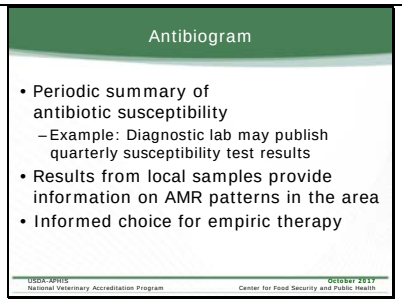

- Multiple methods, both qualitative and quantitative, that can be used to determine a specific bacteria's susceptibility to an antibiotic.

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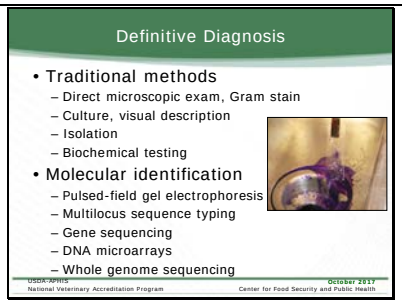

- Molecular identification methods quicker than traditional methods, more costly.

- Developed in a research setting and some may not be commercially available at this time.

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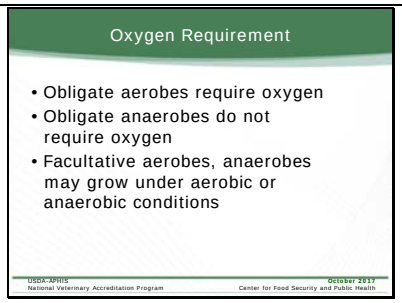

- A bacterium's oxygen requirement can affect its susceptibility to certain antibiotics.

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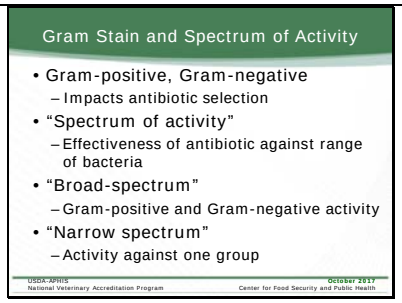

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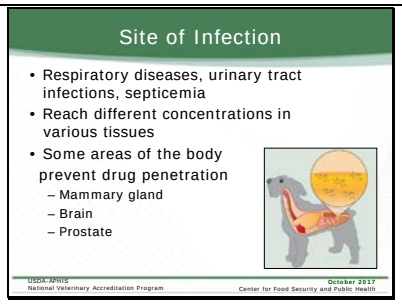

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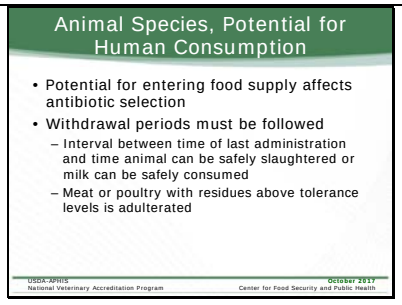

- Only certain antibiotics are approved for use in food producing animals.

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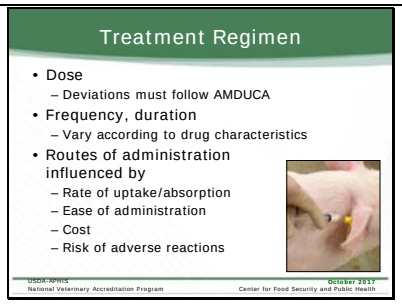

- Treatment regimen includes the dose, frequency, duration of therapy, and route of administration.
- Livestock industry Quality Assurance programs may offer guidance on administration of antibiotics in livestock, including recommended routes and specific techniques to minimize adverse events such as needle breakage.

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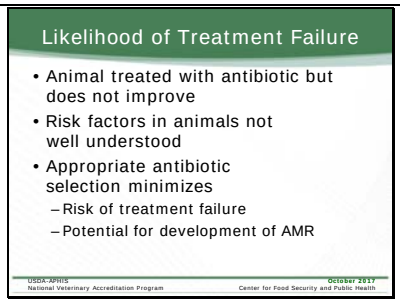

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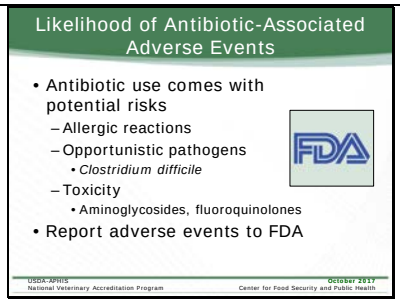

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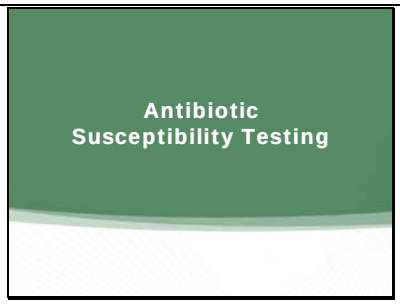

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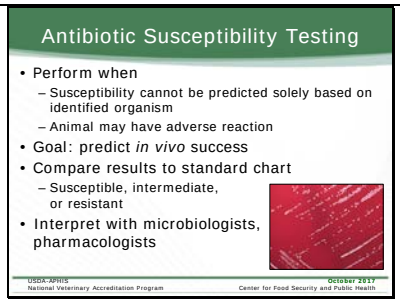

- Comparing susceptibility test results—for a specific isolated bacterium and a specific antibiotic—to a standard interpretation chart, bacteria are then classified
- It is recommended that veterinarians work with clinical microbiologists and pharmacologists to understand and interpret antibiotic susceptibility testing results.
- Common antibiotic susceptibility tests include disk diffusion (Kirby-Bauer), broth microdilution, and antibiotic concentration gradient.

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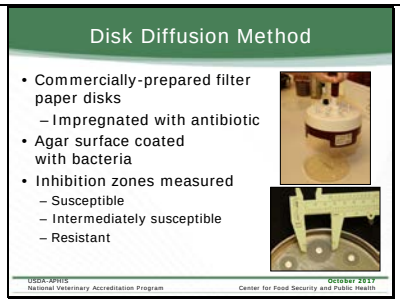

- The disk diffusion method uses 12 commercially-prepared filter paper disks, each impregnated with a standard concentration of a different antibiotic, onto an agar surface coated with the bacterial isolate.
- Zones around the disk are measured as inhibition zones, and are then classified as susceptible, intermediately susceptible, or resistant by comparing measurements to a standard interpretation chart.

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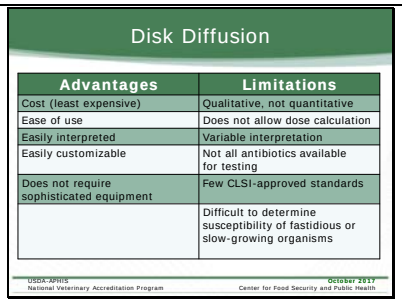

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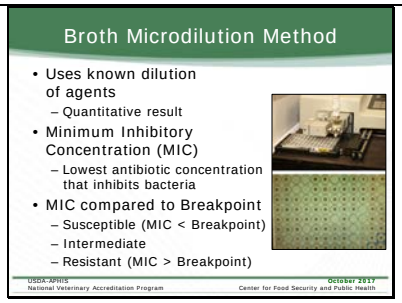

- Provides quantitative result by using known dilution of agents
- Lowest antibiotic concentration at which a bacterial isolate is completely inhibited is recorded as the Minimum Inhibitory Concentration.
- Once determined, MIC is compared to threshold concentration or breakpoint that defines the isolate as susceptible, intermediate, or resistant.
- Breakpoints are validated for a species, specific site of infection, specific pathogen, and specific drug.
- Interpretation of culture and susceptibility report is performed by the submitting veterinarian.
  - Just because lab reports a result for an antibiotic does not mean it can be used in food producing animals.

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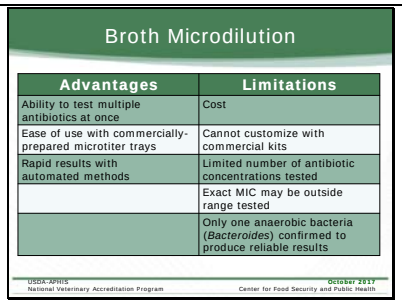

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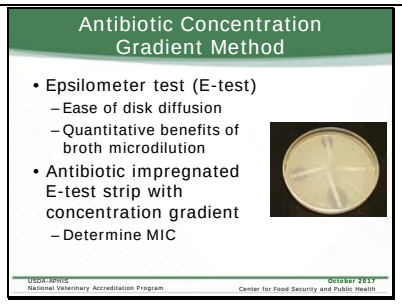

- Combines the ease of disk diffusion with the quantitative benefits of broth microdilution.
- Results for each of the E-test strips are reported with their MIC value and, by using a standard interpretation chart, classified as Susceptible (S), Intermediately susceptible (I), or Resistant (R).

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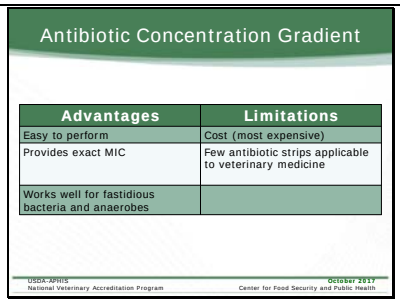

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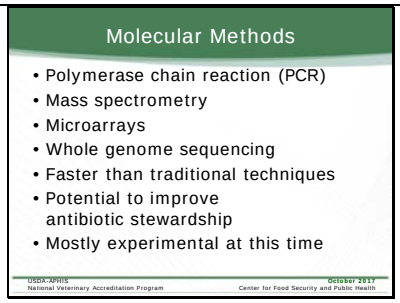

- Because many do not require culturing bacteria, molecular methods can be faster than traditional testing techniques.
  - For example, susceptibility results achieved from PCR could help veterinarians quickly choose the most effective antibiotic for their patient.
- Molecular methods have great potential to improve antibiotic stewardship; however, they remain mostly experimental at this time.
- Susceptibility results obtained from molecular testing may not always correlate with phenotypic resistance.

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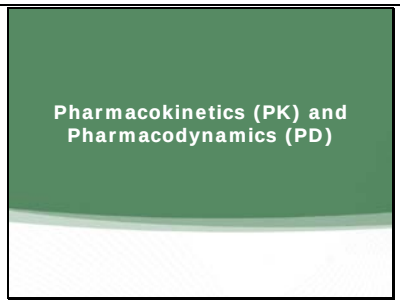

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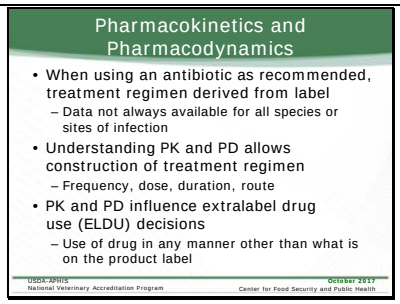

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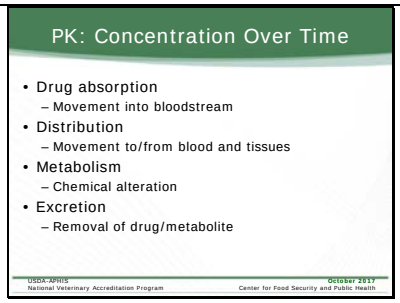

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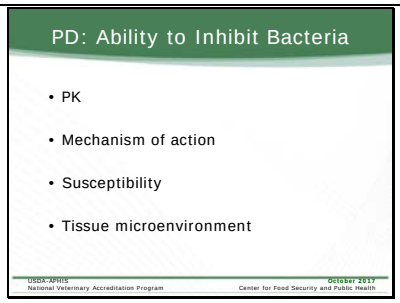

- Ability of an antibiotic to inhibit a bacterium at the site of infection.
- Determined by the interplay of the antibiotic's PK and mechanism of action, as well as bacterial susceptibility and tissue microenvironment at the site of infection.

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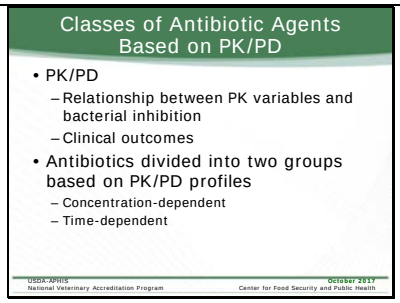

- When used for a specific antibiotic, the term PK/PD represents the relationship between PK variables and bacterial inhibition or killing in the animal.
  - By extension, PK/PD relates to clinical outcomes.

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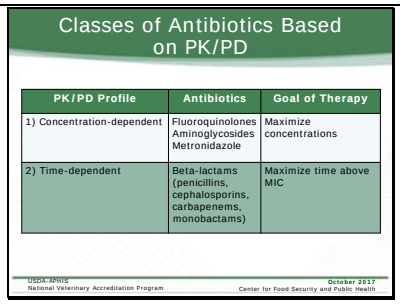

Concentration-dependent antibiotics

- Killing becomes more rapid and profound with increasing drug concentrations.
- To maximize the efficacy of concentration-dependent antibiotics, maximize the *concentration* by *increasing the dose* but keeping dosing *frequency* the same.

Time-dependent antibiotics

- *Time above MIC* is important.
- To maximize efficacy of time-dependent antibiotic agents, the dosing frequency may need to be increased. Increasing the drug concentration does not necessarily improve efficacy.

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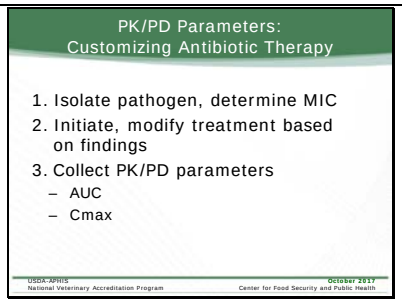

- Multiple benefits to antibiotic therapy customization.
  - Patient-specific and pathogen-specific treatment can lead to better outcomes in individuals.
  - Optimized regimens are also crucial for the prevention of antimicrobial resistance.
- To customize antibiotic therapy for an individual patient,
  - First steps are to isolate the pathogen and determine the MIC.
  - Veterinarian then initiates or modifies to provide the best possible antibiotic therapy based on that information.
- Next, collect PK and PD parameters, which are included on the drug label or package insert that comes with many antibiotics.
  - The most useful parameters to understand include
    - Area Under the Curve (AUC)
      The area under the plasma concentration curve (AUC) is one measure of drug exposure over time.
    - Cmax
      The maximum concentration (Cmax) is the maximum drug concentration in plasma.

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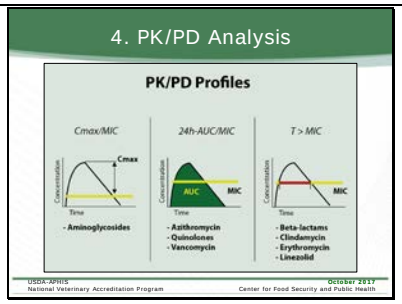

- Next, perform a PK/PD analysis.
  - Using PK/PD parameters found on the drug label and the MIC (determined by antibiotic susceptibility testing), a PK/PD analysis can be performed to optimize the treatment regimen.
  - Values obtained from a PK/PD analysis are compared to a standard to determine if the current antibiotic dose is adequate.

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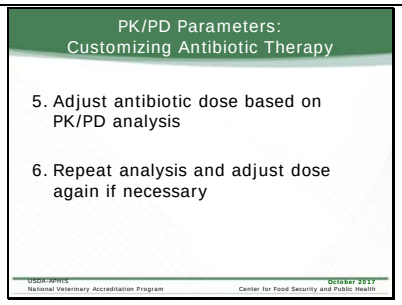

- Based on the PK/PD analysis, the antibiotic dose can be adjusted and the concentrations re-determined to achieve maximum antibiotic efficacy.

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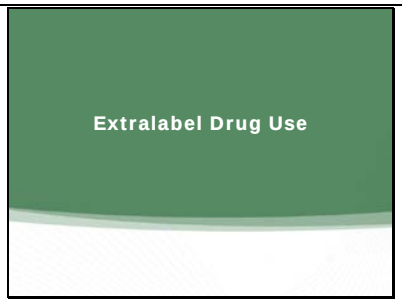

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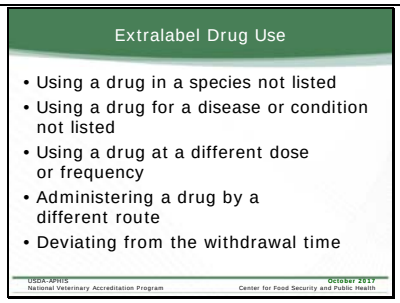

ELDU is the use of an approved drug in a manner that is not in accordance with the approved label.

- using a drug in a species not listed on the label;
- using a drug for a disease or condition not listed on the label;
- using a drug at a different dose or frequency than listed on the label;
- administering a drug by a route not listed on the label; or
- deviating from the labeled withdrawal time.

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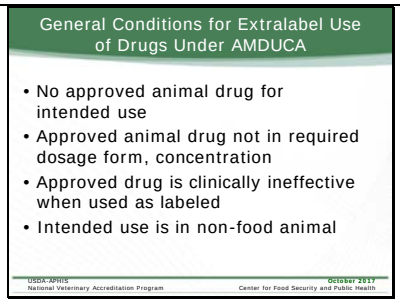

Passed in 1994, AMDUCA allows veterinarians to prescribe certain approved drugs for extralabel use under defined conditions.

Situations in which extralabel use of drugs may be considered include the following:

- There is no animal drug approved for the intended use.
- There is an animal drug approved for the intended use, but the approved drug is not in the required dosage form or concentration.
- The approved drug has been found to be clinically ineffective when used as labeled.
- If the intended use is in a non-food animal, then an approved human drug can be used even if an approved animal drug is available except when the public health is threatened.

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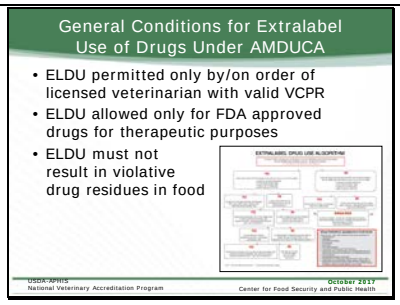

- ELDU is permitted only by or on the order of a licensed veterinarian with a valid Federally-defined VCPR in place.
- ELDU is allowed only for FDA approved animal and human drugs and is intended for therapeutic use only, not production purposes.
- ELDU of an approved drug must not result in violative drug residues in food which could pose a risk to public health.
- The AVMA has provided an algorithm to guide ELDU.

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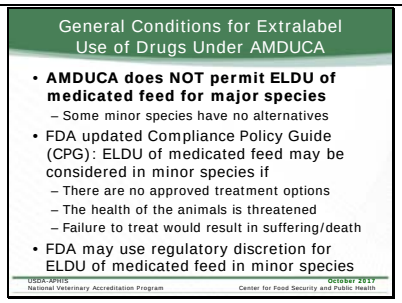

- **AMDUCA does NOT permit ELDU of medicated animal feed, including VFD feed, for major species of food producing animals.**
- However, some minor species have no practical alternatives other than medicated feed.
- The FDA updated the Compliance Policy Guide Section 615.115 (CPG) on December 2, 2016, to address extralabel use of medicated feed, including VFD feed.
    - If conditions and procedures described in the CPG are followed, a veterinarian may consider ELDU of medicated feed **in minor species** if
        - there are no approved treatment options available;
        - the health of the animals is threatened; and
        - failure to treat the animals would result in suffering or death.
- The veterinarian must also provide a written recommendation that includes the medical rationale for ELDU of medicated feed.
- Although not legally permitted, FDA may use regulatory discretion for ELDU of medicated feed in minor species because many commercial medicated feeds that require a VFD are not approved for use in minor species (i.e., are used extralabel).

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- The veterinarian must keep these records for **at least 2 years** as required by Federal law.
    - State recordkeeping requirements may be longer.
- These records must be available at any reasonable time to FDA-designated personnel for copying and verifying.

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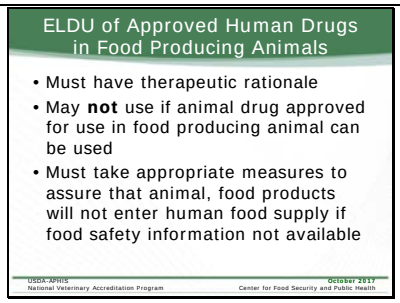

When considering ELDU of an approved human drug in food producing animals, the prescribing veterinarian

- must have a therapeutic rationale for the use;
- may not use an approved human drug in an ELDU manner if an animal drug approved for use in a food producing animal species can be used; and
- must take appropriate measures to assure that the animal and its food products will not enter the human food supply if scientific information on the human food safety aspect of the use of the drug in food producing animals is not available.

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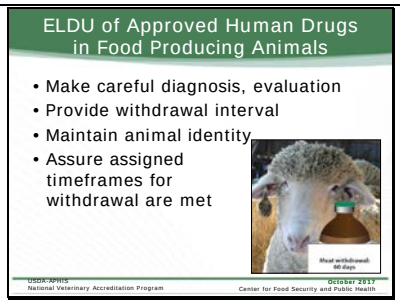

Before prescribing or dispensing an approved animal or human drug for extralabel use in food producing animals, the veterinarian must

- make a careful diagnosis and evaluation of the conditions for which the drug is to be used;
- provide an estimated, scientifically-based, withdrawal interval for the milk, meat, eggs, or other edible products from the treated animal (this information may be obtained by the veterinarian in context of a VCPR from among other sources, scientific literature, academia, or the Food Animal Residue Avoidance Databank (FARAD);
- make sure that the identity of the treated animal or animals is maintained; and
- take measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food producing animal subjected to extralabel treatment.

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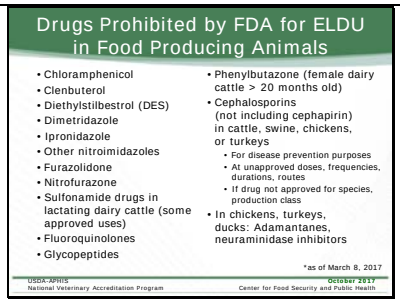

- The FDA also keeps a list of drugs, not limited to antibiotics, prohibited from extralabel use in food producing animals which can be found in the Code of Federal Regulations.
- Some of these drugs are not labeled for use in food producing animals. Make sure to always read the label and use only as approved.

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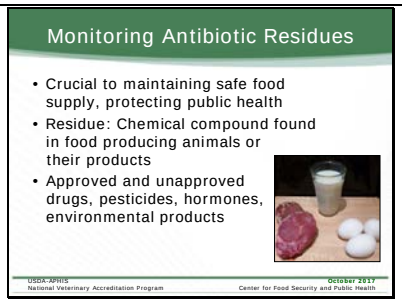

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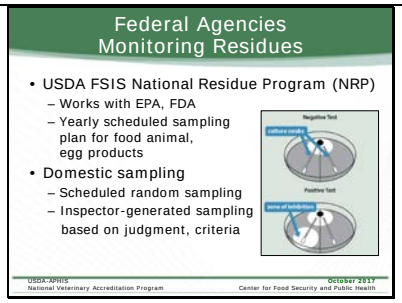

- The USDA Food Safety and Inspection Service protects consumers by ensuring that USDA-inspected meat, poultry, and egg products are safe, wholesome, accurately labeled, and do not contain illegal drug residues.
  - FSIS works with the Environmental Protection Agency (EPA) and FDA to achieve the goals of the National Residue Program (NRP).
  - The NRP provides a yearly scheduled sampling plan for testing chemical compounds in products from food animals and egg products produced domestically or imported into the United States.

- Domestic sampling for residues in meat occurs in one of two ways:
  - Scheduled random sampling of tissues taken from food animals that have passed antemortem inspection; and
  - Inspector-generated sampling where Public Health Veterinarians conduct sampling in-plant on animals suspected of having violative levels of chemical residues. The inspector will select a carcass for sampling based on professional judgment and public health criteria outlined in FSIS directives, including
    - animal disease signs;
    - producer history; or
    - results from random-scheduled sampling.

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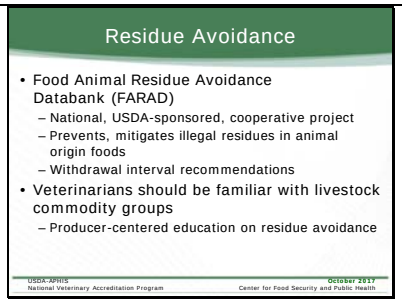

- On the FARAD website, individuals may look up withdrawal period interval recommendations of drugs published in the FARAD digests.
  - If a drug of interest is not listed, a question or request for advice can be submitted via online forms.

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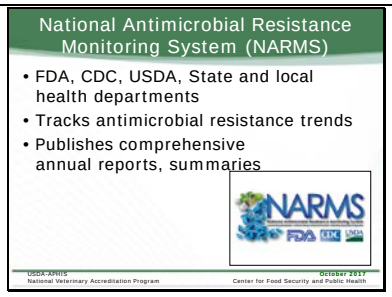

- Antimicrobial resistance trends are monitored throughout the world by various governmental agencies.
- In the United States, the National Antimicrobial Resistance Monitoring System (NARMS) is an interagency partnership among the FDA, the CDC, USDA, and State and local health departments.
- NARMS tracks antimicrobial resistance trends in foodborne and other enteric bacteria. NARMS tests isolates cultured from human clinical specimens (routine surveillance and outbreaks), retail meats, and food producing animals at slaughter.

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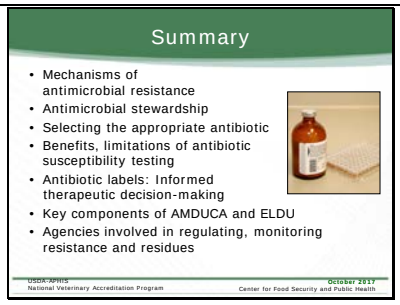

This presentation introduced general concepts about antimicrobial resistance and stewardship and the terms and concepts necessary for veterinarians to make informed decisions for the proper selection and judicious use of antibiotics in animals. The various benefits and limitations of antibiotic susceptibility testing options, as well as correctly interpreting a drug label were presented. A review of the key components of AMDUCA provided information about extralabel use of drugs. Many agencies are involved in antibiotic regulation and antibiotic resistance and residue monitoring.
As new information on use and resistance emerges, the resources presented here can be used to assist in making informed decisions on antibiotic use in animals.

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This informational presentation has been approved expressly to serve as one unit of supplemental training for participants in USDA's National Veterinary Accreditation Program. Please ensure you complete, sign, and retain a certificate stating that you attended this presentation. Contact your VS District Office for more details on renewing your accreditation.

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The content has been reviewed and approved by **USDA-APHIS Legislative and Public Affairs**

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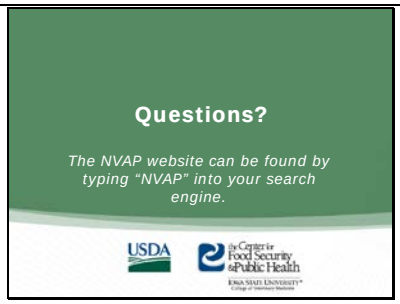

Thank you for your time. I would be glad to answer any questions as time allows. The NVAP website can be found by typing "NVAP" into your search engine.