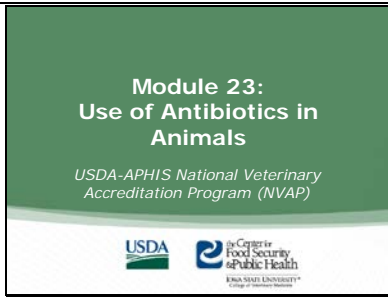


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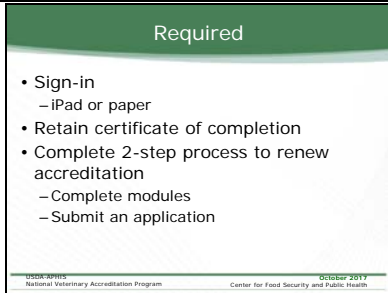


Welcome to **Module 23: Use of Antibiotics in Animals**. This module was developed as supplemental training for the USDA-APHIS National Veterinary Accreditation Program (NVAP) by the Center for Food Security and Public Health at the College of Veterinary Medicine, Iowa State University. The content for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

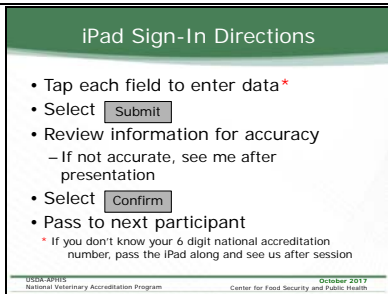
***It is strongly suggested you review the PDF or web version of this module as you are reviewing this PowerPoint prior to your presentation.***

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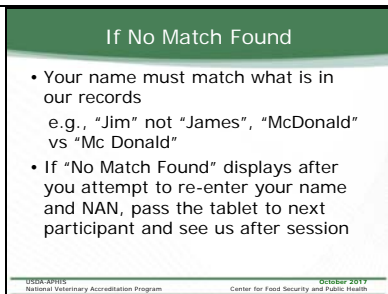
A few important points about the renewal process, first you must sign in to get credit for taking each APHIS Approved Supplemental Training Module. This will either be done using a paper sign in sheet that is being passed around or the iPad that is being passed around. Second, at the end of the presentation 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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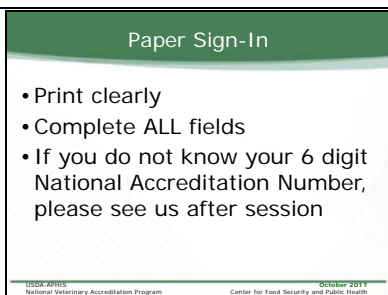
In order for the key pad to display, the participants must first tap the first field on the screen (first name field). This will display the key pad. The participant must then either tap the stylus pen or their finger into each subsequent field on the screen. The user must tap into each field. Enter 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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**Supplemental Training**

- Familiarize accredited veterinarians with animal health regulatory concepts and activities
  - Does not supersede the regulations
- For the most up-to-date regulations and standards, please refer to:
  - Code of Federal Regulations
  - OSHA
  - Occupational health specialist
  - Local VS District Office

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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.

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**Supplemental Training**

- All APHIS Approved Supplemental Training (AASST) modules are also available on our Website with interactive features and links to additional Web resources.
- Type "NVAP" into your search engine e.g., Bing, Google, Yahoo.

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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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**Introduction**

- Antibiotics required in vet medicine
- FDA encouraging judicious use of medically important (for humans) antimicrobial drugs
  - Eliminating the use of medically important antimicrobial drugs for production purposes
  - Providing veterinary oversight of medically important antibiotics in medicated feed via veterinary feed directives (VFDs)


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

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**Overview**

- Mechanisms of antimicrobial resistance
- Antimicrobial stewardship
- Selecting the appropriate antibiotic
- Benefits, limitations of antibiotic susceptibility testing
- Antibiotic labels: Informed therapeutic decision-making
- Key components of Animal Medicinal Drug Use Clarification Act (AMDUCA) and extralabel drug use (ELDU)
- Agencies involved in regulating, monitoring resistance and residues



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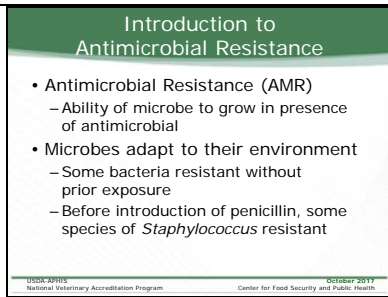
This presentation will help you:

- 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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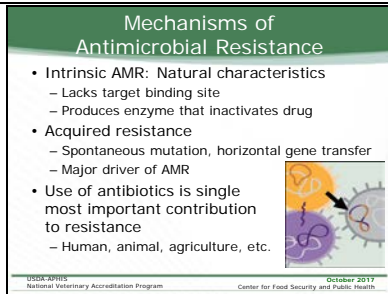


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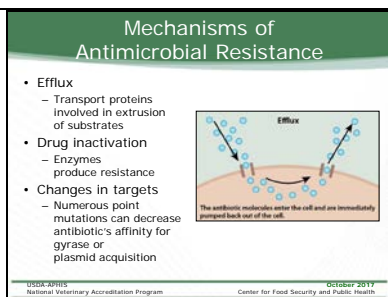
- Microbes constantly adapt to resist the antimicrobials developed to treat them
- Some bacteria are resistant to particular antibiotics or classes of antibiotics without prior exposure to the antibiotic
- Even before the introduction of antibiotics in human medicine, certain species of *Staphylococcus*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

- Restricted uptake
  - Cell walls with high lipid content
- Plasmids
  - Resistance genes for many drugs

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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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**Antimicrobial Resistance: A One Health Problem**

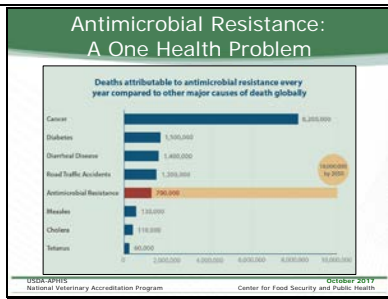
- Illnesses: >2 million human, U.S.
- Deaths: 23,000, U.S.; 700,000, world
- Cost to U.S. economy: \$55 billion
- WHO—AMR is serious threat to global health and security
- Food producing animals serve as reservoirs
  - Spread to humans through direct and indirect routes

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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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### Combating Antimicrobial Resistance

- White House National Action Plan for Combating Antibiotic-Resistant Bacteria
- USDA Antimicrobial Resistance Action Plan
- CDC Antibiotic Resistance Threat Report
- World Organisation for Animal Health (OIE) Antimicrobial Resistance Strategy

- 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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### Judicious Use and Antimicrobial Stewardship

- Critical to slowing development of AMR
- Veterinarians need to work with producers, owners

**Antibiotic Stewardship**

*"Using the right antibiotic at the right time at the right dose for the right duration."*

The White House National Action Plan for Combating Antibiotic Resistant Bacteria, 2015.

- 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 Guidance for Industry #209

- "Judicious Use of Medically Important Antimicrobial Drugs in Food Producing Animals"
- Provides recommendations to limit medically important antimicrobials to uses considered necessary
- Provides recommendations to limit such drugs to uses to include veterinary oversight

- 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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Approved Antibiotic Marketing Status		
OTC	Rx	VFD
Purchased, used without permission of licensed veterinarian	Rx from licensed veterinarian required	Written authorization (VFD order), from licensed veterinarian required
	VCPR required	VCPR required
	Medicated water	Medicated feed (Applies only to drugs FDA approved as VFD)

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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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**Feed Antimicrobials and the Veterinary Feed Directive**

- Animal Drug Availability Act, 1996
- VFD order authorizes the client to obtain and use VFD drugs in or on animal feed
- Client treats in accordance with directions for approved use
- Prior to 1996, medicated animal feed was OTC



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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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**Veterinarian-Client-Patient Relationship (VCPR)**

- Basis for interaction among veterinarians, clients, patients
- Unethical, illegal to prescribe or dispense Rx/VFD drugs
- Required when using drugs in extralabel manner



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**Antibiotic Selection**

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**Antibiotic Selection**

- Characteristics of organism(s)
- Availability of approved antibiotic
- Prevalence of resistance
- Animal species, potential for entering food supply
- Site of infection
- Treatment regimen
- Likelihood of failure, adverse events



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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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**Characteristics of Suspected or Confirmed Bacterial Organism**

- Definitive diagnosis requires laboratory identification
- Therapy based on susceptibility testing
- Empiric treatment is last option, based on
  - “Most likely” pathogen
  - Spectrum of antibiotic susceptibility of suspected pathogen
  - Risks and benefits of treatment



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**Antibiogram**

- Periodic summary of antibiotic susceptibility
  - Example: Diagnostic lab may publish quarterly susceptibility test results
- Results from local samples provide information on AMR patterns in the area
- Informed choice for empiric therapy


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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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**Definitive Diagnosis**

- Traditional methods
  - Direct microscopic exam, Gram stain
  - Culture, visual description
  - Isolation
  - Biochemical testing
- Molecular identification
  - Pulsed-field gel electrophoresis
  - Multilocus sequence typing
  - Gene sequencing
  - DNA microarrays
  - Whole genome sequencing



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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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**Oxygen Requirement**

- Obligate aerobes require oxygen
- Obligate anaerobes do not require oxygen
- Facultative aerobes, anaerobes may grow under aerobic or anaerobic conditions

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

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**Gram Stain and Spectrum of Activity**


- Gram-positive, Gram-negative
  - Impacts antibiotic selection
- "Spectrum of activity"
  - Effectiveness of antibiotic against range of bacteria
- "Broad-spectrum"
  - Gram-positive and Gram-negative activity
- "Narrow spectrum"
  - Activity against one group

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**Site of Infection**

- Respiratory diseases, urinary tract infections, septicemia
- Reach different concentrations in various tissues
- Some areas of the body prevent drug penetration
  - Mammary gland
  - Brain
  - Prostate



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**Animal Species, Potential for Human Consumption**

- Potential for entering food supply affects antibiotic selection
- Withdrawal periods must be followed
  - Interval between time of last administration and time animal can be safely slaughtered or milk can be safely consumed
  - Meat or poultry with residues above tolerance levels is adulterated


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

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**Treatment Regimen**

- Dose
  - Deviations must follow AMDUCA
- Frequency, duration
  - Vary according to drug characteristics
- Routes of administration influenced by
  - Rate of uptake/absorption
  - Ease of administration
  - Cost
  - Risk of adverse reactions



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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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**Likelihood of Treatment Failure**


- Animal treated with antibiotic but does not improve
- Risk factors in animals not well understood
- Appropriate antibiotic selection minimizes
  - Risk of treatment failure
  - Potential for development of AMR

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**Likelihood of Antibiotic-Associated Adverse Events**

- Antibiotic use comes with potential risks
  - Allergic reactions
  - Opportunistic pathogens
    - *Clostridium difficile*
  - Toxicity
    - Aminoglycosides, fluoroquinolones
- Report adverse events to FDA



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**Antibiotic Susceptibility Testing**

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**Antibiotic Susceptibility Testing**

- Perform when
  - Susceptibility cannot be predicted solely based on identified organism
  - Animal may have adverse reaction
- Goal: predict *in vivo* success
- Compare results to standard chart
  - Susceptible, intermediate, or resistant
- Interpret with microbiologists, pharmacologists




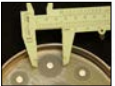
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- Comparing susceptibility test results—for a specific isolated bacterium and a specific antibiotic—to a standard interpretation chart, bacteria are then classified
- It is recommended that veterinarians work with clinical microbiologists and pharmacologists 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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**Disk Diffusion Method**

- Commercially-prepared filter paper disks
  - Impregnated with antibiotic
- Agar surface coated with bacteria
- Inhibition zones measured
  - Susceptible
  - Intermediately susceptible
  - Resistant

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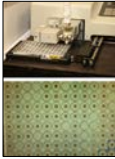
- The disk diffusion method uses 12 commercially-prepared filter paper disks, each impregnated with a standard concentration of a different antibiotic, onto an agar surface coated with the bacterial isolate.
- Zones around the disk are measured as inhibition zones, and are then classified as susceptible,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

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Disk Diffusion	
Advantages	Limitations
Cost (least expensive)	Qualitative, not quantitative
Ease of use	Does not allow dose calculation
Easily interpreted	Variable interpretation
Easily customizable	Not all antibiotics available for testing
Does not require sophisticated equipment	Few CLSI-approved standards
	Difficult to determine susceptibility of fastidious or slow-growing organisms

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Broth Microdilution Method	
<ul style="list-style-type: none"> <li>• Uses known dilution of agents                             <ul style="list-style-type: none"> <li>– Quantitative result</li> </ul> </li> <li>• Minimum Inhibitory Concentration (MIC)                             <ul style="list-style-type: none"> <li>– Lowest antibiotic concentration that inhibits bacteria</li> </ul> </li> <li>• MIC compared to Breakpoint                             <ul style="list-style-type: none"> <li>– Susceptible (MIC &lt; Breakpoint)</li> <li>– Intermediate</li> <li>– Resistant (MIC &gt; Breakpoint)</li> </ul> </li> </ul>	

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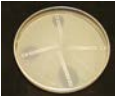
- Provides quantitative result by using known dilution of agents
- Lowest antibiotic concentration at which a bacterial isolate is completely inhibited is recorded as the Minimum Inhibitory Concentration.
- Once determined, MIC is compared to threshold concentration or breakpoint that defines the isolate 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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Broth Microdilution	
Advantages	Limitations
Ability to test multiple antibiotics at once	Cost
Ease of use with commercially-prepared microtiter trays	Cannot customize with commercial kits
Rapid results with automated methods	Limited number of antibiotic concentrations tested
	Exact MIC may be outside range tested
	Only one anaerobic bacteria ( <i>Bacteroides</i> ) confirmed to produce reliable results

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Antibiotic Concentration Gradient Method	
<ul style="list-style-type: none"> <li>• Epsilon test (E-test)                             <ul style="list-style-type: none"> <li>– Ease of disk diffusion</li> <li>– Quantitative benefits of broth microdilution</li> </ul> </li> <li>• Antibiotic impregnated E-test strip with concentration gradient                             <ul style="list-style-type: none"> <li>– Determine MIC</li> </ul> </li> </ul>	

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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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### Antibiotic Concentration Gradient

Advantages	Limitations
Easy to perform	Cost (most expensive)
Provides exact MIC	Few antibiotic strips applicable to veterinary medicine
Works well for fastidious bacteria and anaerobes	

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### Molecular Methods

- Polymerase chain reaction (PCR)
- Mass spectrometry
- Microarrays
- Whole genome sequencing
- Faster than traditional techniques
- Potential to improve antibiotic stewardship
- Mostly experimental at this time

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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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### Pharmacokinetics (PK) and Pharmacodynamics (PD)

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### Pharmacokinetics and Pharmacodynamics

- When using an antibiotic as recommended, treatment regimen derived from label
  - Data not always available for all species or sites of infection
- Understanding PK and PD allows construction of treatment regimen
  - Frequency, dose, duration, route
- PK and PD influence extralabel drug use (ELDU) decisions
  - Use of drug in any manner other than what is on the product label

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### PK: Concentration Over Time

- Drug absorption
  - Movement into bloodstream
- Distribution
  - Movement to/from blood and tissues
- Metabolism
  - Chemical alteration
- Excretion
  - Removal of drug/metabolite

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**PD: Ability to Inhibit Bacteria**

- PK
- Mechanism of action
- Susceptibility
- Tissue microenvironment

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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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**Classes of Antibiotic Agents Based on PK/PD**

- PK/PD
  - Relationship between PK variables and bacterial inhibition
  - Clinical outcomes
- Antibiotics divided into two groups based on PK/PD profiles
  - Concentration-dependent
  - Time-dependent

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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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**Classes of Antibiotics Based on PK/PD**

PK/PD Profile	Antibiotics	Goal of Therapy
1) Concentration-dependent	Fluoroquinolones Aminoglycosides Metronidazole	Maximize concentrations
2) Time-dependent	Beta-lactams (penicillins, cephalosporins, carbapenems, monobactams)	Maximize time above MIC

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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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**PK/PD Parameters:  
Customizing Antibiotic Therapy**

1. Isolate pathogen, determine MIC
2. Initiate, modify treatment based on findings
3. Collect PK/PD parameters
  - AUC
  - Cmax

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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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**4. PK/PD Analysis**

**PK/PD Profiles**

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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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**PK/PD Parameters:  
Customizing Antibiotic Therapy**

5. Adjust antibiotic dose based on PK/PD analysis
6. Repeat analysis and adjust dose again if necessary

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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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**Extralabel Drug Use**

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**Extralabel Drug Use**

- Using a drug in a species not listed
- Using a drug for a disease or condition not listed
- Using a drug at a different dose or frequency
- Administering a drug by a different route
- Deviating from the withdrawal time

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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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**General Conditions for Extralabel Use of Drugs Under AMDUCA**

- No approved animal drug for intended use
- Approved animal drug not in required dosage form, concentration
- Approved drug is clinically ineffective when used as labeled
- Intended use is in non-food animal

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

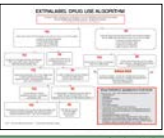
Situations in which extralabel use of drugs may be considered include the following:

- 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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**General Conditions for Extralabel Use of Drugs Under AMDUCA**

- ELDU permitted only by/on order of licensed veterinarian with valid VCPR
- ELDU allowed only for FDA approved drugs for therapeutic purposes
- ELDU must not result in violative drug residues in food



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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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**General Conditions for Extralabel Use of Drugs Under AMDUCA**

- **AMDUCA does NOT permit ELDU of medicated feed for major species**
  - Some minor species have no alternatives
- FDA updated Compliance Policy Guide (CPG): ELDU of medicated feed may be considered in minor species if
  - There are no approved treatment options
  - The health of the animals is threatened
  - Failure to treat would result in suffering/death
- FDA may use regulatory discretion for ELDU of medicated feed in minor species

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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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**ELDU Recordkeeping Requirements**

- Records must include:
  - Name of drug, active ingredient(s)
  - Condition treated
  - Species of treated animal(s)
  - Dosage, route, duration
  - Number of animals treated
  - Animal's identification
  - Withdrawal, withholding, discard time(s)
- Keep records **for at least 2 years**
- Records available at any time



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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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**ELDU Labeling Requirements**

- Name, address of veterinarian (pharmacy)
- Name of drug, active ingredient(s)
- Directions for use
  - Class/species/identification, dosage, frequency, route, duration
- Animal identification
  - Individual or group/pen
- Withdrawal intervals
- Cautionary statements



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**ELDU of Approved Human Drugs in Food Producing Animals**

- Must have therapeutic rationale
- May **not** use if animal drug approved for use in food producing animal can be used
- Must take appropriate measures to assure that animal, food products will not enter human food supply if food safety information not available

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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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**ELDU of Approved Human Drugs in Food Producing Animals**

- Make careful diagnosis, evaluation
- Provide withdrawal interval
- Maintain animal identity
- Assure assigned timeframes for withdrawal are met



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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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**Drugs Prohibited by FDA for ELDU in Food Producing Animals**

<ul style="list-style-type: none"> <li>• Chloramphenicol</li> <li>• Clenbuterol</li> <li>• Diethylstilbestrol (DES)</li> <li>• Dimetridazole</li> <li>• Iprnidazole</li> <li>• Other nitroimidazoles</li> <li>• Furazolidone</li> <li>• Nitrofurazone</li> <li>• Sulfonamide drugs in lactating dairy cattle (some approved uses)</li> <li>• Fluoroquinolones</li> <li>• Glycopeptides</li> </ul>	<ul style="list-style-type: none"> <li>• Phenylbutazone (female dairy cattle &gt; 20 months old)</li> <li>• Cephalosporins (not including cephalirin) in cattle, swine, chickens, or turkeys                             <ul style="list-style-type: none"> <li>• For disease prevention purposes</li> <li>• At unapproved doses, frequencies, durations, routes</li> <li>• If drug not approved for species, production class</li> </ul> </li> <li>• In chickens, turkeys, ducks: Adamantanes, neuraminidase inhibitors</li> </ul>
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\*as of March 8, 2017

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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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**Residues and Resistance**

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**Monitoring Antibiotic Residues**

- Crucial to maintaining safe food supply, protecting public health
- Residue: Chemical compound found in food producing animals or their products
- Approved and unapproved drugs, pesticides, hormones, environmental products

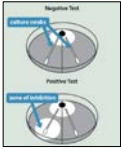


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**Federal Agencies Monitoring Residues**

- USDA FSIS National Residue Program (NRP)
  - Works with EPA, FDA
  - Yearly scheduled sampling plan for food animal, egg products
- Domestic sampling
  - Scheduled random sampling
  - Inspector-generated sampling based on judgment, criteria



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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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**Residue Avoidance**

- Food Animal Residue Avoidance Databank (FARAD)
  - National, USDA-sponsored, cooperative project
  - Prevents, mitigates illegal residues in animal origin foods
  - Withdrawal interval recommendations
- Veterinarians should be familiar with livestock commodity groups
  - Producer-centered education on residue avoidance

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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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**National Antimicrobial Resistance Monitoring System (NARMS)**

- FDA, CDC, USDA, State and local health departments
- Tracks antimicrobial resistance trends
- Publishes comprehensive annual reports, summaries

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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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**Summary**

- Mechanisms of antimicrobial resistance
- Antimicrobial stewardship
- Selecting the appropriate antibiotic
- Benefits, limitations of antibiotic susceptibility testing
- Antibiotic labels: Informed therapeutic decision-making
- Key components of AMDUCA and ELDU
- Agencies involved in regulating, monitoring resistance and residues

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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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**Questions?**

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USDA Center for Food Security and Public Health Iowa State University College of Veterinary Medicine

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.