

# **RESISTING RESISTANCE**

## **FDA'S ANTIPARASITIC RESISTANCE MANAGEMENT STRATEGY (ARMS)**

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# Overview

## **Antiparasitic resistance is an issue for grazing livestock in the United States.**

- ▣ How bad is it?
- ▣ How do we manage it & prevent it?
- ▣ What is FDA-CVM's role in this?



# Goals for this webinar

## To understand:

- ✓ the potential threat of antiparasitic resistance in grazing livestock in the U.S.
- ✓ the paradigm shift between parasite elimination and parasite control
- ✓ the challenges that exist with establishing appropriate species-specific parasite control management strategies
- ✓ what FDA-CVM is doing to address the issue of antiparasitic resistance in grazing livestock



# Roadmap for this webinar

- Who we are/our purpose
- History of CVM's Public Meeting on Antiparasitic Resistance March 2012
- Antiparasitic Resistance: what, who, why, how
- What CVM's role is to address the problem
- What CVM has done, what we'd like to do



# FDA-CVM

- Within FDA, the Center for Veterinary Medicine (CVM) regulates animal drugs (including anthelmintics), animal feed, and veterinary devices.
- We make sure an animal drug is safe and effective before approving it
- We monitor the safety and effectiveness of animal drugs on the market



# FDA-CVM

**Our mission:**

*“Protecting human and animal health.”*

**Our vision:**

*“Excellence. Innovation. Leadership.”*

**Promoting the sustainable use of anthelmintics is within both our mission and vision.**

# Office of New Animal Drug Evaluation (ONADE)

- Reviews information submitted by drug sponsors to determine if a new animal drug is approvable
- For approval, a new animal drug must:
  - ▣ Be effective
  - ▣ Be safe for:
    - Target animal species
    - Human user
    - Human consumption (for food animals only)
  - ▣ Be consistently manufactured, processed, and packaged (identity, strength, quality, and purity)
  - ▣ Be properly labeled



# Office of New Animal Drug Evaluation (ONADE)

- **For food animal drugs:**
  - ▣ Human food safety is established
  - ▣ Have established analytical method(s) to quantify drug residues in human food derived from animal products (meat, milk, eggs, honey)

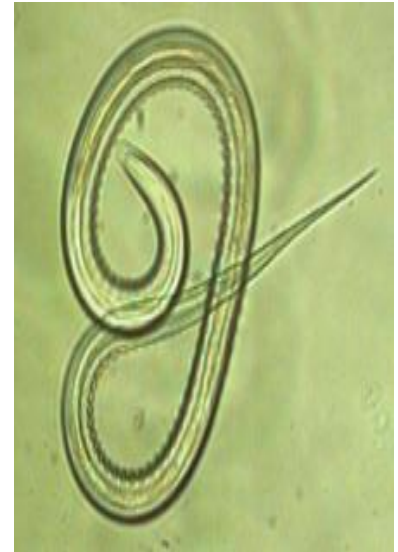


# Office of Surveillance and Compliance (OSC)

- Assure that approved, marketed animal drugs remain safe and effective through:
  - RISK DETECTION (Pharmacovigilance)
    - Examination of Adverse Drug Experience Reports (ADEs)
    - Literature review
  - RISK COMMUNICATION
    - Review and revise animal drug product labels
      - Post-approval Experience section (PAE)
    - Regulate Promotional Activities
    - Confer with animal drug sponsors

# CVM's Public Meeting

- March 2012, CVM held a Public Meeting: “Antiparasitic Drug Use and Resistance in Ruminants and Equines”
- Hosted 7 internationally-recognized veterinary parasitologists/pharmacologists



# CVM's Public Meeting

## Topics discussed:

- ✓ Current state of anthelmintic resistance in the U.S. and worldwide
- ✓ How to diagnose and define anthelmintic resistance
- ✓ Ways anthelmintic drugs can be used (alone versus in combination) to maximize effectiveness and minimize resistance

# CVM's Public Meeting

Need for **paradigm shift** in the way veterinarians and producers view parasites:



**From parasite  
elimination to  
parasite control**

# State of anthelmintic resistance

## Small ruminants:

- ▣ The HOT complex is the primary concern
- ▣ Since 2003, resistance well-documented and widespread, mostly in Southeast U.S.

**First case of TOTAL  
anthelmintic failure  
in U.S. in goats: 2004**



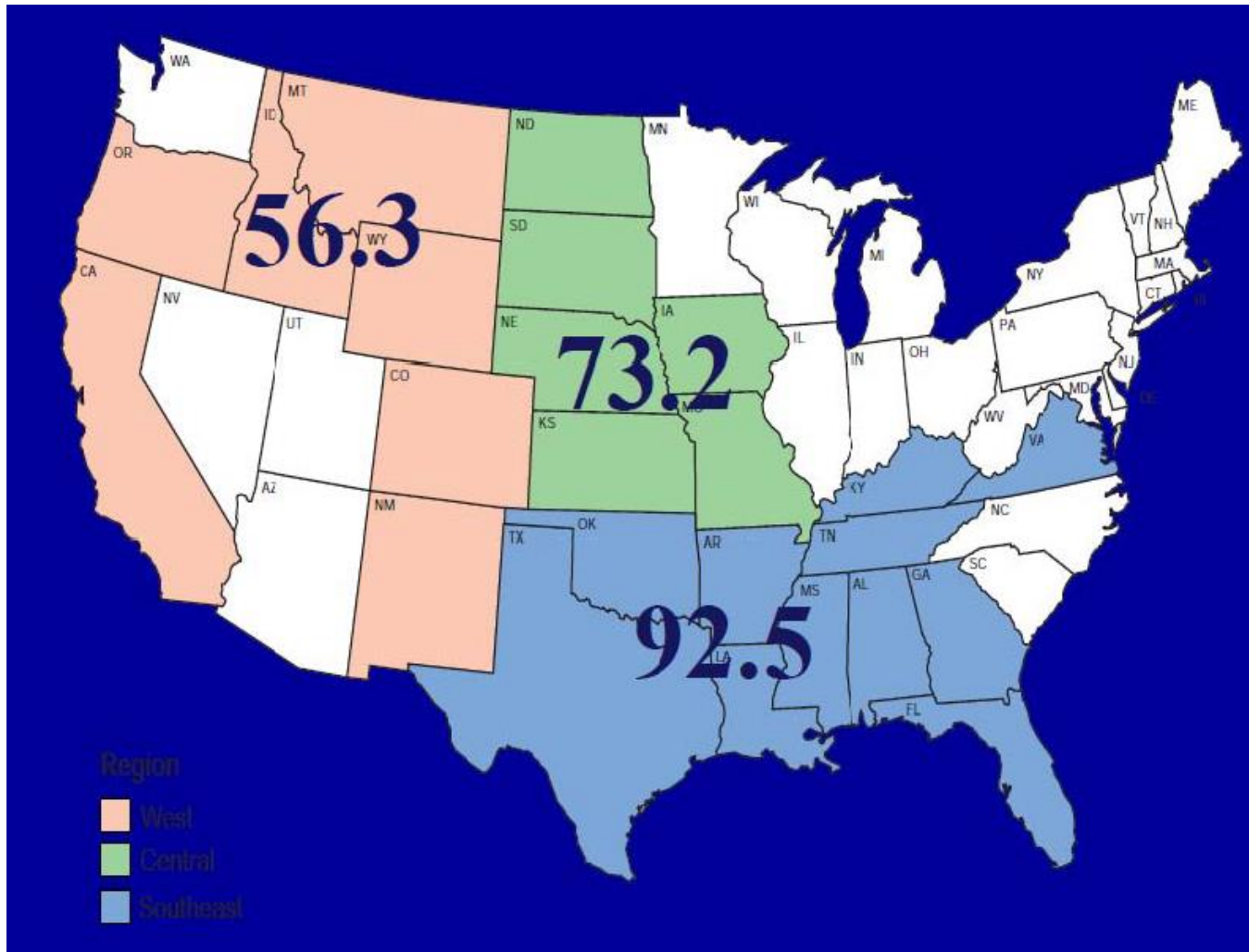
# State of anthelmintic resistance



## Cattle:

- 2009 data confirmed resistance to macrocyclic lactones across 9 states
- **Cooperia spp.** resistance becoming a problem

# Beef 2007-08 NAHMS survey: 14 d post-treatment % reduction



# Concerns for *Cooperia* species

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- In the past, ***Cooperia* spp.** considered less pathogenic than ***Ostertagia***
- ***Cooperia* spp.** now the most commonly seen cattle nematode in the U.S.



# State of anthelmintic resistance

## Horses:

- Resistance in small strongyles to benzimidazoles is high throughout the country
- Overall equine nematode resistance to dewormers in U.S. uncertain



# Uncertainty!

**Parasitologists uncertain of the prevalence and distribution of current resistance in the U.S. in livestock species, particularly beef cattle and horses**



# First reports of resistance (Kaplan 2004)

Drug	Host	Year of initial drug approval *not necessarily in US	First published report of resistance
<b>Benzimidazoles</b>			
Thiabendazole	Sheep	1961	1964
	Horse	1962	1965
<b>Imidothiazoles-tetrahydropyrimidines</b>			
Levamisole	Sheep	1970	1979
Pyrantel	Horse	1974	1996
<b>Macrocyclic lactones</b>			
Ivermectin	Sheep	1981	1988
	Horse	1983	2002
Moxidectin	Sheep	1991	1995
	Horse	1995	2003

# History of U.S. anthelmintic use

## □ Recent history

- Ivermectin and other macrocyclic lactones (MLs) were highly effective
- Producers became heavily dependent on drugs for control of parasites

## □ Resistance is emerging

- Parasite populations are changing
- MLs and other anthelmintics becoming less effective against some parasites (dependent on many factors)

# Factors contributing to resistance

- **Parasite factors**

- Genetics, biology

- **Management factors**

- Treating too frequently
- Treating entire herd
- “Strategic” deworming
- Under-dosing

- **Drug factors**

- Sub-therapeutic drug levels after initial therapeutic level



# Diagnosis of resistance:

## Fecal Egg Count Reduction Test (FECRT)

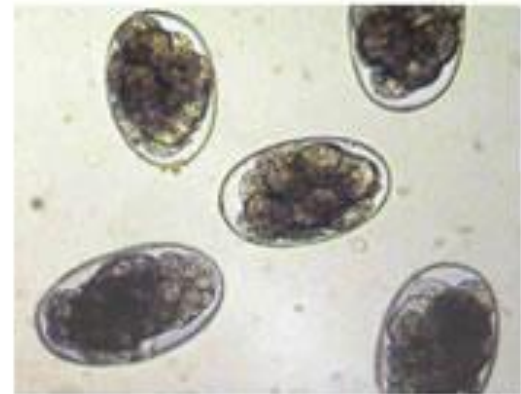
### Current on-farm **GOLD STANDARD**

It has its limitations, species differences

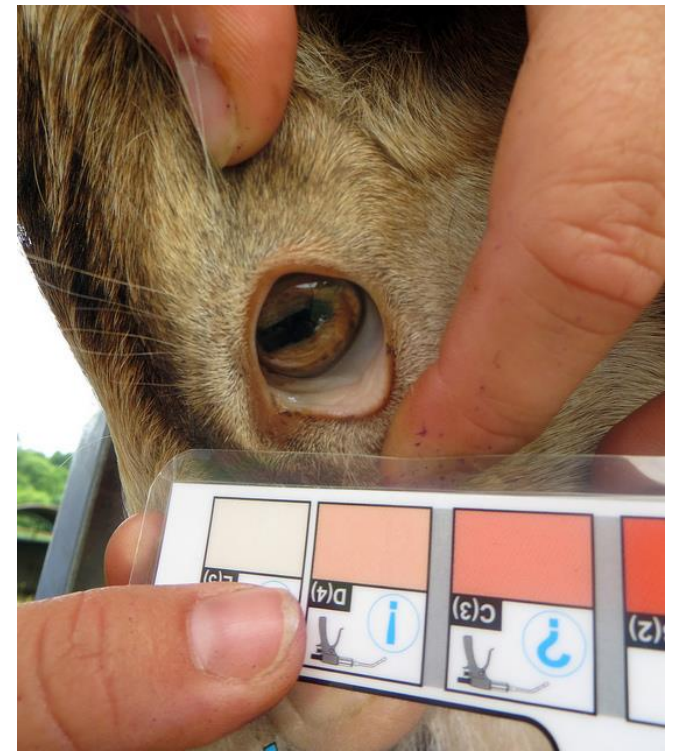
**NOT PERFECT**

□ **Other methods:**

- Larval development assay
- PCR
- Egg hatch test



# FAMACHA



# Management options





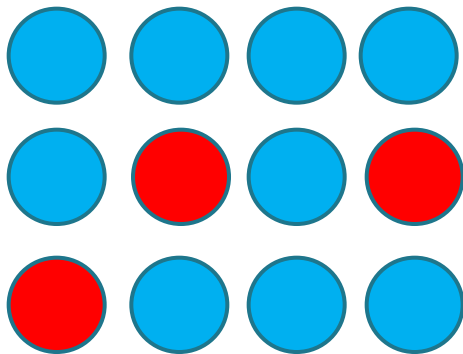
# Refugia

## The proportion of the total parasite population that is not selected for anthelmintic treatment

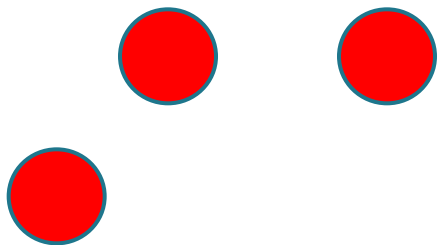
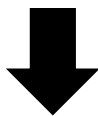
- ▣ Those parasites that are in “**refuge**” from the drug
- ▣ Therefore have no selection pressure to develop resistance
- ▣ A benefit of refugia is to maintain a proportion of susceptible parasites on the farm

# Refugia

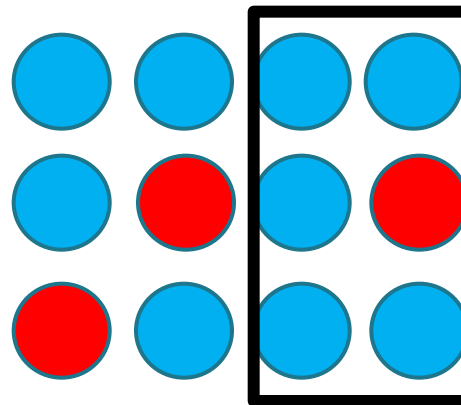
Parasite population  
within the herd:



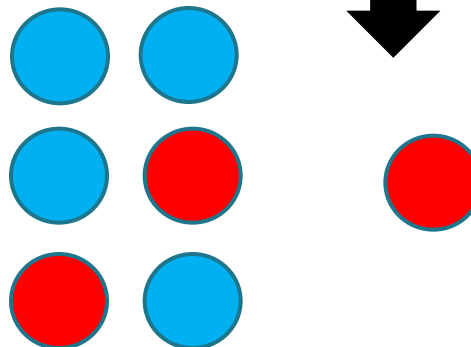
Treat entire herd, so  
no refugia is  
preserved.



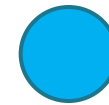
Parasite population  
within the herd:



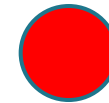
Treat only 50% of herd,  
so some refugia is  
preserved.



Key:



Susceptible  
parasite



Resistant  
parasite

**SOLUTION  
TO  
POLLUTION  
IS DILUTION!**

# Over-the-counter vs RX

- Resistance detection is more complicated than first thought – need for veterinary involvement?
- Majority of U.S. large animal anthelmintics are OTC
- The Denmark Model
  - ▣ Pros and cons



# Not one size fits all

- **Challenges for making grazing livestock parasite control recommendations**
  - Data lacking
  - Differences in parasite biology between livestock species (warm weather vs cold weather worms)
  - Differences in production – particularly beef cattle stratifications
    - Cow/calf
    - Stocker/backgrounders
    - Feedlot

# Not one size fits all



# Managing resistance

- ✓ Use clinical signs and diagnostics to determine what worms are on the farm. Base management and treatment decisions on this data.
- ✓ Use anthelmintics that are effective based on recent diagnostics.
- ✓ Follow the label directions for correct dosing and administration.
- ✓ Anthelmintics are not approved for performance, weight gain, or feed efficiency.

**Long term benefit versus short term gain**

# Managing resistance



**Ideally, identify and focus on animals  
that are the highest shedders**

**Remember the 80/20 rule**

**80%** of parasite eggs are shed by

**20%** of the animals in a flock or herd

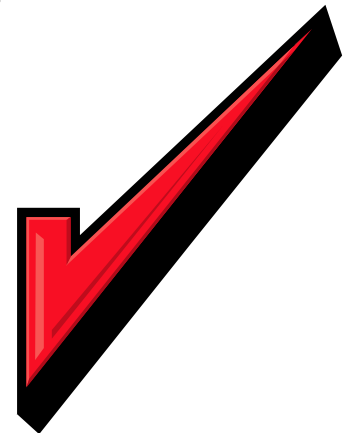


# Managing resistance

- Breed innate resistance into your herd
- Cull heavy shedders, those lacking innate resistance
- If identifying heavy shedders is impractical (or culling is unacceptable, i.e. pet livestock, horses)
  - ▣ Target treatment toward animals at greatest risk of illness from parasites
  - ▣ Small ruminants with high FAMACHA scores should be treated

# Managing resistance

- Weigh animals to avoid under-dosing
- Maintain adequate treatment records
- Quarantine new livestock
- Reduce livestock density on pastures



# Combination dewormers?

Multiple studies have shown that appropriately chosen combinations of anthelmintics from different drug families, when used appropriately, have the potential to slow the development of resistance.

**In regulatory terms, these are combinations with highly/completely overlapping indications**

None are approved in the U.S. yet.

We encourage drug companies to investigate such combos for approval.

# Role of education

- Currently, vet school curricula and CE venues are not emphasizing parasite management and many vets are not aware of the emergence of resistance in the U.S., especially in cattle.
- This is where collaboration with vet schools, extension agents, AVMA, and other professional organizations comes in.



# CVM'S ARMS initiative

## Antiparasitic Resistance Management Strategy (ARMS)

- CVM's initiative to promote sustainable use of anthelmintic drugs in grazing livestock species
- Launched in September 2012
- 3-pronged approach:
  - ▣ Education
  - ▣ Research
  - ▣ Regulation



# Species covered by ARMS



- ARMS covers the primary grazing livestock species in the U.S.: cattle, goats and sheep, and horses
- ARMS currently does **not** cover cats and dogs, swine, poultry, or aquaculture

# Progress – what's been done so far?

- Pathway for approval of combination anthelmintics
- Website
- Brochure
- Speaking engagements
- *JAVMA* Commentary
- *Veterinary Parasitology* Special Issue
- Inter-agency and international communication
- Monitoring scientific literature and clinical data



# Brochure

## Helpful Information for Veterinarians

### Antiparasitic Resistance in Cattle and Small Ruminants in the United States: How to Detect It and What to Do About It

#### Introduction

Internal parasite infections and external parasite infestations harm animal health and can result in significant production losses in food-producing species, such as cattle, sheep, and goats.

Antiparasitic animal drugs are used to treat and control parasitic infections and infestations in animals. The parasites that a given drug is effective against are listed in the indication on the drug's label.

Antiparasitic resistance is the genetic ability of parasites to survive the effects of an antiparasitic drug to which they were previously susceptible. Antiparasitic resistance becomes a problem when an increasing percentage of a parasite population carries resistance genes, allowing the parasites to survive treatment with an antiparasitic drug that has been effective in the past.

Australia, New Zealand, South Africa, and South America have struggled with antiparasitic resistance in livestock species for the past few decades. Recent scientific data indicate antiparasitic resistance is now emerging in livestock species in the United States.

#### Refugia

After an animal is treated with an antiparasitic drug, the susceptible parasites die and the resistant parasites survive to pass on resistance genes to their offspring. If not enough susceptible parasites remain in the environment and in the animal, they cannot dilute the increase in resistant parasites that occurs after treatment. This scenario occurs when there is a lack of *refugia*.

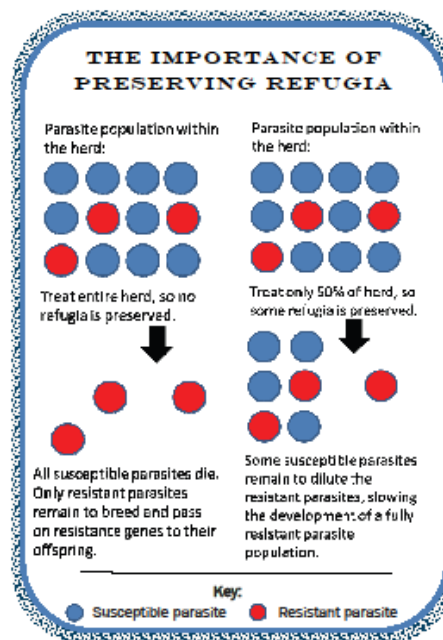
#### What is refugia?

Refugia is the proportion of the total parasite population that is not selected for antiparasitic drug treatment—essentially, those parasites that are in “refuge” from the drug. Therefore, there's no selection pressure on these parasites to develop resistance. Refugia maintains a proportion of susceptible parasites on the farm and includes:

- Parasites in untreated animals, called host-based refugia.
- Eggs and larvae already on the pasture when the animals are treated, called environmental refugia.
- Life stages of the parasite that are unaffected by drug treatment, such as some larval stages.

#### Why is preserving refugia important?

Preserving refugia maintains drug-sensitive (susceptible) parasites. The presence of some drug-sensitive parasites decreases (dilutes) the proportion of resistant parasites within the parasite population on a farm.





# Website

The screenshot shows the FDA website page for Antiparasitic Resistance. The header includes the FDA logo, the text "U.S. Food and Drug Administration Protecting and Promoting Your Health", and navigation links for "A to Z Index", "Follow FDA", and "FDA Voice Blog". A search bar is located in the top right. Below the header is a navigation menu with tabs for "Home", "Food", "Drugs", "Medical Devices", "Radiation-Emitting Products", "Vaccines, Blood & Biologics", "Animal & Veterinary", "Cosmetics", and "Tobacco Products". The main content area is titled "Animal & Veterinary" and "Antiparasitic Resistance". A left sidebar contains a "Safety & Health" menu with options like "Antiparasitic Resistance", "Report a Problem", "Recalls & Withdrawals", "Product Safety Information", "Animal Feed Safety System (AFSS)", "Antimicrobial Resistance", "Animal Cloning", and "Frequently Asked Questions". The main text defines antiparasitic resistance, explains its threat to animal health, and lists factors contributing to it. It also mentions FDA's Center for Veterinary Medicine and its Antiparasitic Resistance Management Strategy (ARMS). An "Additional Information" box lists three related documents: "FDA's Public Meeting on Antiparasitic Drug Use and Resistance in Ruminants and Equines", "FDA's Public Meeting on Antiparasitic Drug Use and Resistance in Ruminants and Equines - An Overview (PDF - 384KB)", and "Helpful Information for Veterinarians - Antiparasitic Resistance in Cattle and Small Ruminants in the United States: How to Defeat it and What to do about it (PDF - 784KB)". The footer contains the FDA logo, contact information, and a list of links for "Accessibility", "Contact FDA", "Careers", "FDA Basics", "FOIA", "No Fear Act", "Site Map", "Transparency", and "Website Policies".

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## Animal & Veterinary

Home | Animal & Veterinary | Safety & Health

### Safety & Health

- Antiparasitic Resistance
- Report a Problem
- Recalls & Withdrawals
- Product Safety Information
- Animal Feed Safety System (AFSS)
- Antimicrobial Resistance
- Animal Cloning
- Frequently Asked Questions

## Antiparasitic Resistance

### What is antiparasitic resistance?

Antiparasitic resistance is the genetic ability of parasites to survive treatment with an antiparasitic drug that was generally effective against those parasites in the past. After an animal is treated with an antiparasitic drug, the susceptible parasites die and the resistant parasites survive to pass on resistance genes to their offspring.

Antiparasitic resistance poses a significant threat to animal health and can result in production losses in food-producing species. Researchers have documented antiparasitic resistance in grazing species, such as cattle, small ruminants (sheep and goats), and horses, both globally and within the United States.

Many factors contribute to antiparasitic resistance, including the biology of the parasite; the immune status of the host animal; treatment practices; drug properties; and certain livestock management practices.

### What is FDA's Center for Veterinary Medicine doing about antiparasitic resistance?

To help combat this emerging problem, the FDA's Center for Veterinary Medicine started the Antiparasitic Resistance Management Strategy (ARMS). The strategy promotes sustainable use of approved antiparasitic drugs in cattle, small ruminants, and horses. Sustainable use will help ensure that antiparasitic drugs remain effective for as long as possible, thereby slowing the development of antiparasitic resistance in grazing species in the United States.

### Additional Information

- FDA's Public Meeting on Antiparasitic Drug Use and Resistance in Ruminants and Equines
- FDA's Public Meeting on Antiparasitic Drug Use and Resistance in Ruminants and Equines - An Overview (PDF - 384KB)
- Helpful Information for Veterinarians - Antiparasitic Resistance in Cattle and Small Ruminants in the United States: How to Defeat it and What to do about it (PDF - 784KB)

Page Last Updated: 05/02/2013  
Note: If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#).

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# Regulatory Roles



- We are **not** proposing removing any anthelmintics from the market
- Recognize that **antiparasitic** resistance and **antimicrobial** resistance are very separate issues

# Thinking ahead



# Thinking ahead

## What would we like to see in 5 to 10 years?

- ❑ Development of novel anthelmintics
- ❑ Approval of combination anthelmintics
- ❑ Producers implementing sustainable parasite management practices
- ❑ Producers partnering with veterinarians when making parasite management decisions
- ❑ Currently approved anthelmintics remain effective

# What we still need

- **Practical (evidence-based) guidelines for producers, especially in beef cattle**
- **Continued research:**
  - ▣ Validate methods
  - ▣ U.S. data on cattle refugia
  - ▣ Better diagnostics
  - ▣ Prevalence data for resistance in all grazing species in U.S. (greatest need for data in cattle and horses)

# What can you do?

- ❑ **Report suspected cases of lack of effectiveness to CVM**
  - ▣ Lack of effectiveness is an adverse event and should be reported
  - ▣ Include as much data as possible (FECRT, doses, age/use of animal, production scheme, etc.)



# What CVM continues to do



- Work with industry to provide the most up-to-date recommendations on labeling
- Monitor promotional materials for misleading claims, omission of risk information

# Final thoughts



- Ultimately, we want to ensure that approved anthelmintics remain effective for as long as possible
- This should be a shared goal between CVM and stakeholders (industry, veterinarians, producers, researchers, owners)



# Resources

- CVM website:  
<http://www.fda.gov/animalveterinary/safetyhealth/ucm350360.htm>
- Docket for public meeting:  
<http://www.fda.gov/animalveterinary/resourcesforyou/ucm318015.htm>
- Public meeting overview:  
<http://www.fda.gov/downloads/AnimalVeterinary/ResourcesforYou/UCM344299.pdf>
- Brochure:  
<http://www.fda.gov/downloads/animalveterinary/resourcesforyou/ucm347442.pdf>
- *Antiparasitic Resistance and Grazing Livestock in the United States* J Am Vet Med Assoc 2014 May 1;244(9):1020-2.
- Veterinary Parasitology Special Issue Vol 204, Issues 1-2, Pages 1-80 (30 July 2014)

# Contacts

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