

# Antiparasitic Resistance Management Strategy

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# Goals for this meeting

- CVM will introduce current FDA-CVM activity related to antiparasitic resistance in livestock in the US (ARMS initiative)
- CVM will provide overview of information presented at the Public Meeting
- CVM will invite members to engage in dialogue regarding antiparasitic resistance, outreach, areas of potential collaboration between AVMA and USAHA

# Overview

- Antiparasitic resistance in livestock and horses is a threat in the US
- CVM sees the opportunity to address this threat early (ARMS initiative)
- Initiative includes potential collaboration with professional organizations (e.g. AVMA, AABP, AAEP, etc.), other federal Agencies (e.g. USDA), and international outreach

# Antiparasitic Resistance as an emerging US issue

- Reports of antiparasitic resistance in small ruminants, cattle, and equines in the US are increasing
- No longer just a problem in other countries
- We need to address it early, before it becomes widespread and significantly affects animal health and the US food supply

# History of US antiparasitic use

- In 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 antiparasitics becoming less effective against some parasites

# History of US antiparasitic use

- Paradigm shift is required if we want to preserve effective anthelmintics in the future
  - Management changes
  - Encourage appropriate use of anthelmintics
  - Some countries have already made regulatory changes to address this

# Prompted into action

- In Australia/New Zealand, some South American countries, and South Africa, there are documented cases of resistance in all classes of antiparasitics. The U.S. is not there yet – this is our chance to implement changes before we get there.

# FDA-CVM's role

- Within the FDA, the Center of Veterinary Medicine's mission is “protecting human and animal health.”
- Our vision is: “Excellence. Innovation. Leadership.”

**Proactive involvement tackling antiparasitic resistance falls under both our mission and vision.**



# FDA-CVM: Office of New Animal Drug Evaluation

- Reviews information submitted by drugs sponsors to determine if a new animal drug should be approved
- For approval, a new animal drug for must:
  - Be shown to be effective
  - Be determined safe for:
    - Human food (excluding non-food animals)
    - Target animal species
    - Environment
    - Human user
  - Have established analytical method(s) to quantify drug residues in edible animal products (food animal drugs)
  - Be consistently manufactured, processed, and packaged (identity, strength, quality, and purity)
  - Be appropriately labeled

# FDA-CVM: Office of Surveillance and Compliance

- Monitors marketed animal drugs, food additives, and veterinary devices to assure their safety and effectiveness
- Pharmacovigilance – detection, assessment and evaluation of adverse reactions to drugs
  - Adverse drug experience (ADE) reporting:
    - Identification of safety signals and effectiveness issues
    - Mandatory for drug sponsors; voluntary for practitioners and other users

# Public Meeting Summary

- March 5 – 6, 2012, CVM hosted a public meeting to discuss the following topics regarding antiparasitic drug use and resistance in ruminants and equines:
  - The current state of anthelmintic resistance in the US and worldwide
  - Tools for the evaluation of antiparasitic resistance
  - The evaluation of the effectiveness of drugs against resistant parasites
  - The scientific rationale for the use of combinations of antiparasitic drugs in ruminants and equines

# Public Meeting

- This was a successful first step in addressing the emergence of antiparasitic resistance in the US
  - 7 international veterinary parasitologists on the panel
  - Members of industry, veterinary practitioners, and members from across CVM attended

# Public Meeting

- **The current state of anthelmintic resistance in the US**
  - Small Ruminants: the HOT complex is the primary concern, since 2003, APR well-documented and widespread, mostly in Southeast US
  - Cattle: 2009 data confirmed APR to macrocyclic lactones across 9 states, *Cooperia* resistance becoming problem
  - Horses: APR of small strongyles to BZDs is high throughout country, overall prevalence in US is uncertain

# Public Meeting

- Factors contributing to APR
  - **Parasite factors**
    - Genetics, biology
  - **Management factors**
    - Treating too frequently
    - Treating entire herd
    - “Strategic” deworming
    - Under dosing
  - **Drug factors**
    - Persistent effects

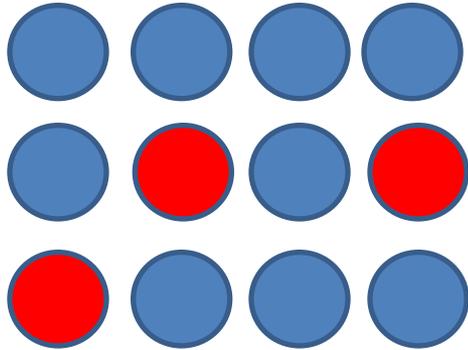


# Public Meeting

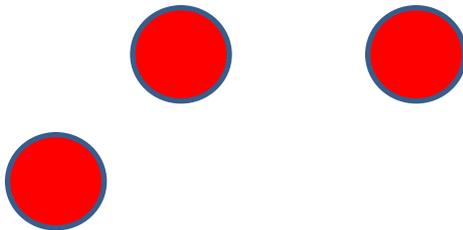
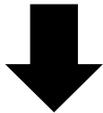
- **Refugia** – the proportion of the total parasite population that is not selected for antiparasitic drug treatment
  - Those parasites that are in “refuge” from the drug
  - Have no selection pressure to develop resistance
  - Refugia maintains a proportion of susceptible parasites on the farm

# The Importance of Preserving Refugia

Parasite population within the herd:

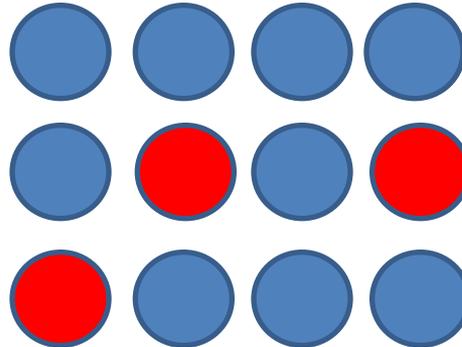


Treat entire herd, so no refugia is preserved.

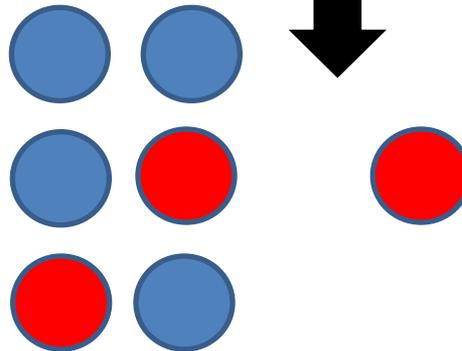
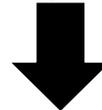


All susceptible parasites die. Only resistant parasites remain to breed and pass on resistance genes to their offspring.

Parasite population within the herd:



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



Some susceptible parasites remain to dilute the resistant parasites, slowing the development of a fully resistant parasite population.

**Key:**

-  Susceptible parasite
-  Resistant parasite

# Public Meeting

- Anthelmintic combinations
  - Appropriate combos have been demonstrated to slow the development of APR when used judiciously
  - Regulatory challenge: currently no approved anthelmintic combinations containing active ingredients with highly or completely overlapping indications on the market in the US

# Public Meeting

- OTC versus RX
  - Including a veterinarian in a farm's parasite management program is beneficial
    - Education is key
  - The Denmark Model
    - Pros and cons

# Public Meeting

- **Diagnosing APR**

- FECRT considered the “practical gold standard” for on-the-farm diagnosis
- Limitations, species differences
- Other methods:
  - LDA
  - PCR
  - Egg hatch test



# Public Meeting

- Challenges of defining resistance
  - 90%? 95%?, or more aptly, a change in FECRT on a single farm over time
  - Characterizing resistant isolates
  - Designing studies to support the approval of “resistant claims”

# Public Meeting

- Pour-ons
  - Studies are showing that the use of transdermal anthelmintics is contributing to APR for a variety of reasons:
    - Least accurate dosing method, inappropriate application practices
    - Variable transdermal absorption rates



# Public Meeting

- The role of education
  - Currently, vet school curricula and CE are not emphasizing parasite management. Many vets are not aware of the emergence of APR in the US, especially in cattle.
  - This is where collaboration with vet schools, extension agents, AVMA, other professional organizations comes in.
    - Small ruminant industry is very proactive and knowledgeable (FAMACHA training, etc.)
    - Equine industry making proactive strides (recent white paper from AAEP)

# The Future and CVM

- Antiparasitic Resistance Management Strategy (ARMS)
  - Roadmap of how CVM can be a leader in slowing the development of antiparasitic resistance in grazing species in the US by collaboration with other regulatory offices and agencies, and outside organizations
    - Education
    - Research
    - Regulatory Path

# ARMS

- What ARMS does not cover:
  - Small animals (dogs and cats)
  - Swine, poultry, aquaculture

# Education

- This is our best tool to introduce the concept of “parasite *management*” versus the traditional view of “parasite *elimination*”
- Efforts within the last year:
  - Survey
  - Brochure
  - CVM’s website
  - Encourage education in other venues (meetings, etc)

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

# 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*.

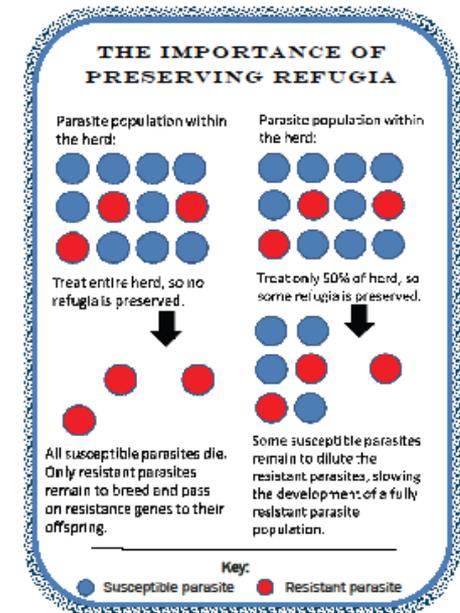
### What is refugia?

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.





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## 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 Detect it and What to do about it \(PDF - 784KB\)](#)

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# Research

- Many aspects of antiparasitic resistance are still unknown
- This is the most challenging aspect (funding, etc.)
  - Work with our Office of Research
  - Collaborate with universities, industry, and USDA/ARS, possibly EPA
  - Tap into research conducted by international regulatory agencies
  - CVM's survey

# Regulatory Path

- Combining current science with our regulatory framework to provide safe and effective drugs for veterinarians and producers
  - Public Meeting
- Work with other international regulators to determine the best strategy to address antiparasitic resistance, learn from others' experiences

# Questions for Discussion

- Does USAHA have a role in tackling antiparasitic resistance concerns?
- Are you already tackling this topic? If so, how? What has worked or not worked? Have you met any resistance from constituents?
- What do you see as obstacles toward education on APR?
- Are there opportunities for collaboration between CVM/ARMS and USAHA in APR?

# ARMS Contacts



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