ANTIPARASITIC RESISTANCE
US FDA’S EXPERIENCE

Aimee Phillippi-Taylor, DVM, DABVP (Equine)
Overview

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

- What is FDA-CVM’s experience thus far?
- What is FDA-CVM’s role now and in the future?
Within FDA, the Center for Veterinary Medicine (CVM) regulates animal drugs (including antiparasitics), 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.
Promoting the sustainable use of antiparasitics is within both our mission and vision.
# FDA Approved Antiparasitics: Sheep, Goats, and Cattle

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiabendazole</td>
<td>Sheep, goats, cattle</td>
</tr>
<tr>
<td>Morantel tartrate</td>
<td>Goats, cattle</td>
</tr>
<tr>
<td>Albendazole</td>
<td>Sheep, goats, cattle</td>
</tr>
<tr>
<td>Fenbendazole</td>
<td>Goats, wild sheep, cattle</td>
</tr>
<tr>
<td>Levamisole</td>
<td>Sheep and cattle</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Sheep and cattle</td>
</tr>
<tr>
<td>Moxidectin</td>
<td>Sheep and cattle</td>
</tr>
<tr>
<td>Oxfendazole</td>
<td>Cattle</td>
</tr>
<tr>
<td>Doramectin</td>
<td>Cattle</td>
</tr>
<tr>
<td>Eprinomectin</td>
<td>Cattle</td>
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</tbody>
</table>

*This list is current as of September 2015

**Not all products may be currently marketed*
FDA Approved Antiparasitics:  
Horses

- Several older products are approved (including organophosphates and piperazine combinations), but are no longer marketed.

- Commonly marketed, approved products include:

<table>
<thead>
<tr>
<th>Active ingredients</th>
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<tbody>
<tr>
<td>Ivermectin (±praziquantel)</td>
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<tr>
<td>Moxidectin ((±praziquantel)</td>
</tr>
<tr>
<td>Pyrantel pamoate</td>
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<tr>
<td>Pyrantel tartrate (administered daily in feed)</td>
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<tr>
<td>Fenbendazole (approved at 2 dose regimens)</td>
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<tr>
<td>Oxibendazole</td>
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<tr>
<td>Other benzimidazoles are approved but not commonly used</td>
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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 antiparasitic resistance in the U.S. and worldwide

✓ How to diagnose and define antiparasitic resistance

✓ Ways antiparasitic drugs can be used (alone versus in combination) to maximize effectiveness and minimize resistance
Multiple studies have shown that appropriately chosen combinations of antiparasitics 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 currently approved in the U.S. We encourage drug companies to investigate such combos for approval.
CVM’S ARMS initiative

Antiparasitic Resistance Management Strategy (ARMS)

- CVM’s initiative to promote sustainable use of anthiparasitic 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.
Reaching Out

- A primary goal of ARMS is to spread the word regarding antiparasitic resistance and sustainable use of antiparasitic drugs in livestock species

- Education is a priority
  - ARMS keeps informed on the most recent research worldwide: includes regular review of published literature, and attending scientific meetings (AAVP and WAAVP)
  - Speaking opportunities – in the US and beyond
    - Recent US examples include at AVMA 2014, 2015
    - VICH Veterinary Outreach Forum February 2013
    - OIE Focal Points meeting (today’s presentations)
Progress – what’s been done so far?

- Pathway for approval of combination antiparasitics
- Website
- Brochure
- Speaking engagements
- *JAVMA* Commentary
- *Veterinary Parasitology* Special Issue
- Inter-agency and international communication
- Monitoring scientific literature and clinical data
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 Antiparasite 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 - 584KB)
- Helpful Information for Veterinarians ... Antiparasitic Resistance in Cattle and Small Ruminants in the United States: How to Diagnose It and What to do about It (PDF - 784KB)
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.

THE IMPORTANCE OF PRESERVING REFUGIA

Parasite population within the herd:

- Treat entire herd, so no refugia is preserved.
- Treat only 50% of herd, so some refugia is preserved.
- All susceptible parasites die. Only resistant parasites remain to breed and pass on resistance genes to their offspring.
- Some susceptible parasites remain to dilute the resistant parasites, slowing the development of a fully resistant parasite population.

Key: Yellow: Susceptible parasite Red: Resistant parasite
Progress – More to come

- Collaboration with USDA APHIS allowing for collection of fecal samples during the 2015 Equine National Animal Health Monitoring System (NAHMS) survey
  - Goal is to estimate prevalence of strongyle resistance in equids on a national and regional basis

Participants answered questions to assess:
- Awareness of antiparasitic resistance
- Commonly used strategies for detecting and managing antiparasitic resistance
- Opinions on labeling and label statements

Our goal is to publish the results
Regulatory Roles

- We are not proposing the removal of any antiparasitics from the market.
- Recognize that antiparasitic resistance and antimicrobial resistance are separate issues.
Thinking ahead

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

What would we like to see in 5 to 10 years?
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 CVM continues to do

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

- Ultimately, we want to ensure that approved antiparasitics remain effective for as long as possible
- This should be a shared goal not only in the US, but throughout the world for the benefit of animal and public health
Resources

- CVM website: http://www.fda.gov/animalveterinary/safetyhealth/ucm350360.htm
- Docket for public meeting: http://www.fda.gov/animalveterinary/resourcesforyou/ucm318015.htm
- Antiparasitic Resistance and Grazing Livestock in the United States
- Veterinary Parasitology Special Issue Vol 204, Issues 1-2, Pages 1-80 (30 July 2014)
Contacts

- **Aimee Phillippi-Taylor, DVM** (equine)
  aimee.phillippi-taylor@fda.hhs.gov
- **Anna O’Brien, DVM** (cattle, small ruminants)
  anna.obrien@fda.hhs.gov