Goals for this presentation

- Provide overview of antiparasitic resistance in grazing livestock, particularly small ruminants
- Provide information on antiparasitic resistance presented at CVM’s Public Meeting, March 2012
- Introduce current CVM activity related to antiparasitic resistance in livestock in the US (ARMS initiative)
Antiparasitic resistance as an emerging US issue

- Reports of antiparasitic resistance in small ruminants, cattle, and equines in the US are increasing
  - This is not new for sheep producers
- No longer just a problem in other countries
- Howell (2008) study in SE US, 46 sheep/goat farms, 48% had resistance to all 3 major antiparasitic classes
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
### First reports of resistance (Kaplan 2004)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Host</th>
<th>Year of initial drug approval</th>
<th>First published report of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzimidazoles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiabendazole</td>
<td>Sheep</td>
<td>1961</td>
<td>1964</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1962</td>
<td>1965</td>
</tr>
<tr>
<td><strong>Imidothiazoles-tetrahydropyrimidines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levamisole</td>
<td>Sheep</td>
<td>1970</td>
<td>1979</td>
</tr>
<tr>
<td>Pyrantel</td>
<td>Horse</td>
<td>1974</td>
<td>1996</td>
</tr>
<tr>
<td><strong>Avermectin-milbemycins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Sheep</td>
<td>1981</td>
<td>1988</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1983</td>
<td>2002</td>
</tr>
<tr>
<td>Moxidectin</td>
<td>Sheep</td>
<td>1991</td>
<td>1995</td>
</tr>
<tr>
<td></td>
<td>Horse</td>
<td>1995</td>
<td>2003</td>
</tr>
</tbody>
</table>
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
In Australia/New Zealand, some South American countries, and South Africa, there are documented cases of resistance in all classes of antiparasitics. The same is true for small ruminants in the US.
FDA-CVM’s role

- Within the FDA, the Center for Veterinary Medicine’s mission is “protecting human and animal health.”

Proactive involvement tackling antiparasitic resistance falls under both our mission and vision.
FDA-CVM: Office of New Animal Drug Evaluation

- Reviews information submitted by drug sponsors to determine if a new animal drug should be approved

For approval, a new animal drug must:
- Be shown to be effective
- Be determined safe for:
  - Human food (excluding non-food animals)
  - Target animal species
  - 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
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
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
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
Factors contributing to APR

- **Parasite factors**
  - Genetics, biology
- **Management factors**
  - Treating too frequently
  - Treating entire herd
  - "Strategic" deworming
  - Under dosing
- **Drug factors**
  - Persistent effects
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
Refugia

- Implementation in sheep versus cattle
- How to convince producers to embrace this concept?
- New Zealand experience
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 (sheep versus cattle)
  - Other methods:
    - LDA
    - PCR
    - Egg hatch test
Challenges of defining resistance
  - 90%? 95%?; or more aptly, a change in FECRT on a single farm over time
  - Characterizing resistant isolates
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
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, industry, 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
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
  - Presentations at various stakeholder meetings
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 - 794KB)
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
- CVM’s survey, NAHMS 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
ARMS Contacts

- Michelle Kornele, DVM (michelle.kornele@fda.hhs.gov)
- Anna O’Brien, DVM (anna.obrien@fda.hhs.gov)
- Aimee Phillippi-Taylor, DVM (aimee.phillippi-taylor@fda.hhs.gov)
  - http://www.fda.gov/AnimalVeterinary/SafetyHealth/ucm350360.htm
Questions?