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## **FDA's Public Meeting on Antiparasitic Drug Use and Resistance in Ruminants and Equines – An Overview**

**Meeting Dates:** March 5 and 6, 2012

**Hosted by:** FDA Center for Veterinary Medicine's Office of New Animal Drug Evaluation

**Goal of Meeting:** To discuss the current status of antiparasitic resistance in ruminants and equines in the U.S. The discussions focused on how to detect and monitor antiparasitic resistance and ways antiparasitic drugs can be used, alone or in combination, to maximize effectiveness and minimize resistance.

**Expert Speakers:** Seven internationally recognized veterinary parasitologists and pharmacologists gave presentations.

- Roger Prichard, BSc, PhD, FASP – Professor, Institute of Parasitology, McGill University, Montreal, Canada
- Ray Kaplan, DVM, PhD, DACVM, DEVPC – Professor, Department of Infectious Diseases, College of Veterinary Medicine, University of Georgia, Athens, Ga.
- Louis Gasbarre, PhD – U.S. Department of Agriculture's Agricultural Research Service, retired
- Carlos Lanusse, Méd Vet., Dr. Cs. Vet., PhD, DECVPT – Professor, Laboratorio de Farmacología, Universidad Nacional del Centro de la Provincia de Buenos Aires, Argentina
- Dave Leathwick, BSc (Hons), PhD – Research scientist in parasitology, Hopkirk Research Institute, Palmerston North, New Zealand
- Craig Reinemeyer, DVM, PhD, DACVM – Founder and President, East Tennessee Clinical Research, Inc., Rockwood, Tenn.
- Timothy Geary, BSc, PhD – Professor and Director, Institute of Parasitology, McGill University, Montreal, Canada

For an overview of each topic covered at the meeting, please click on the links below. For more detailed information, please view the meeting transcript and PowerPoint presentations at: <http://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm318015.htm>.

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**Common Antiparasitic Drug Classes for Ruminants and Equines**

Common Antiparasitic Drug Classes for Ruminants and Equines

<b>Antiparasitic Drug Class</b>	<b>Examples</b>
Benzimidazoles	Thiabendazole, albendazole, fenbendazole, oxfendazole, oxibendazole
Imidazothiazoles	Levamisole
Tetrahydropyrimidines	Morantel tartate, pyrantel
Macrocyclic lactones	Ivermectin, doramectin, eprinomectin, moxidectin
Piperazines	Piperazine
Isoquinolones	Praziquantel

Note: This table wasn't presented at the public meeting and is included here for clarification purposes only. Also, not all drugs are approved for all species, and some drugs may no longer be marketed in the U.S. For approved species and indications, see each drug's label or check [Animal Drugs @ FDA](#).

## Antiparasitic Resistance – Definitions and Current Status

### What is antiparasitic resistance?

Antiparasitic resistance can be defined several ways, such as the ability of parasites to:

- Survive treatment with an antiparasitic drug that is generally effective against the same parasite species at the same dose and against the same stage of infection. This ability is due to changes in gene frequency, mostly because of mutations, rather than pre-existing resistance genes. The genetic mutations conferring resistance are then passed on to subsequent generations of parasites.
- Tolerate the approved dose of an antiparasitic drug to which they were previously susceptible due to genetic mutations.

### **Antiparasitic resistance is a widespread problem in small ruminants, cattle, and horses. In each group of animals, what is the current status of resistance in the U.S. and internationally?**

#### *U.S.*

- Small Ruminants: The three big parasites of concern are *Haemonchus contortus* (barber pole worm), *Teladorsagia circumcincta* (stomach worm), and *Trichostrongylus colubriformis* (black scour worm). Since 2003, antiparasitic resistance in small ruminants has been well-documented and widespread in the U.S., with most resistance in the southeastern states. Often, the parasites are resistant to multiple classes of antiparasitic drugs.
- Cattle: Data compiled in 2009 from the results of fecal egg count reduction tests confirmed antiparasitic resistance, mainly to macrocyclic lactones, in U.S. cattle in nine states in the Southeast and the West. Resistance to *Cooperia* species is becoming more of a problem across the country.
- Horses: The resistance of small strongyles to benzimidazoles is high throughout the country. Also, in one study of horse farms in the southern U.S., about 50 percent had parasites resistant to pyrantel based on data from fecal egg count reduction tests. Resistance to ivermectin in both *Parascaris equorum* (roundworm) and *Oxyuris equi* (pinworm) may be increasing. However, the overall prevalence of antiparasitic resistance in U.S. horses is uncertain.

#### *Internationally*

Widespread resistance to benzimidazoles and macrocyclic lactones is seen in small ruminants. Antiparasitic resistance is much less in cattle than in small ruminants, but it's increasing. In horses, there's considerable resistance to benzimidazoles, and more recently, resistance to macrocyclic lactones has been seen.

## **Contributing Factors to the Development of Antiparasitic Resistance**

### **What factors contribute to the development of antiparasitic resistance?**

Parasite, management, and drug factors all contribute to the development of antiparasitic resistance.

#### *Parasite Factors*

Multiple mechanisms may confer resistance to a parasite population. Resistance to some antiparasitic drug classes may involve more than one mechanism. Parasite factors involved in resistance development include:

- Genetics of the parasite. The development of antiparasitic resistance can be due to mutations in a single gene or multiple genes in the parasite's genome. Resistance development further depends on the genes' heritability—how much the resistance can be attributed to genetic factors versus environmental factors—and whether the genes are dominant or recessive. Although dominant and recessive genes are passed on at the same rate, resistance due to dominant genes is phenotypically seen sooner in the parasite population than resistance due to recessive genes. This is because the offspring need to inherit only one dominant copy of the gene from one parent to express resistance, rather than two recessive copies (one from each parent).
- Biology of the parasite. The parasite's life cycle, relationship with the host, and number of eggs produced influence how fast resistance develops.
- Parasite fitness. The ability of the parasite to survive and reproduce also influences the development of resistance. The greater a parasite's fitness, the more likely it is to survive. Resistant parasites may have greater fitness, meaning they are more likely to survive and reproduce—both with and without drug exposure—than susceptible parasites.

#### *Management Factors*

Management factors can be divided into practices that increase selection pressure for antiparasitic resistance (increase the frequency of resistance genes) and practices that decrease selection pressure (decrease the frequency of resistance genes).

Practices that increase selection pressure for antiparasitic resistance include:

- Treating too often. Each treatment with an antiparasitic drug eliminates parasites with susceptible genotypes. With increased treatment frequency, there are more opportunities to kill susceptible parasites and leave behind resistant ones. The result is a greater proportion of resistant parasites in the total parasite population.

- Treating the entire herd. Treating the entire herd at the same time eliminates the susceptible parasites from all animals at once. This increases the proportion of resistant parasites in the total parasite population.
- Strategic deworming. Strategic deworming is treating when most parasites are in the host animal rather than in the environment. Treatment is most commonly done in the spring and fall, after a harsh winter and a hot, dry summer have killed the eggs and larvae on the pasture. After treatment, resistant parasites are left in the host animal and produce eggs that harbor resistance genes. The host animal then sheds these eggs onto the pasture. Because the overall numbers of eggs and larvae on the pasture are low at the time of strategic deworming, the proportion of resistant eggs goes up, resulting in an increased frequency of resistance genes in the total parasite population.
- Having inadequate quarantine procedures. Newly purchased animals may harbor resistant parasites. If new arrivals are introduced into a flock or herd without following adequate quarantine procedures (such as, prior to introduction, treating new animals with an antiparasitic drug and performing a [fecal egg count reduction test](#) to confirm treatment was effective), they may shed eggs from resistant parasites, increasing the frequency of resistance genes on the farm.
- Under-dosing. Treating animals with less than the approved dose of an antiparasitic drug exposes the parasite population to a sub-therapeutic drug level, leading to resistance.

Practices that decrease selection pressure for antiparasitic resistance include:

- Choosing the “right” antiparasitic drug. This choice is an informed decision based on diagnostics, such as the [fecal egg count reduction test](#), to determine which drug is most effective against the parasites present on a farm. By using the most effective drug or combination of drugs, one treatment kills more parasites, leaving behind fewer surviving resistant parasites to pass on resistance genes.
- Preserving [refugia](#). “The solution to pollution is dilution!” and “Dilute the undesirables!”
- Using antiparasitic drugs along with non-chemical control methods, such as good pasture management practices, adequate quarantine procedures, and routine culling of heavy egg shedders.

#### *Drug Factors – “The Perils of Persistency”*

The antiparasitic drug’s behavior both in the animal and in the parasite impacts how quickly resistance develops. One important aspect of the drug’s behavior is whether it’s short- or long-acting. Long-acting drugs that persist in the animal’s body a long time after initial treatment tend to select for resistance more quickly than short-acting drugs. Long-acting drugs may “fuel the fire” of antiparasitic resistance by not only putting selection pressure on the parasites present in the animal at the time of treatment (head selection), but also on parasite larvae ingested after treatment (tail selection). Also, as the level of a long-acting drug declines in an animal’s body over

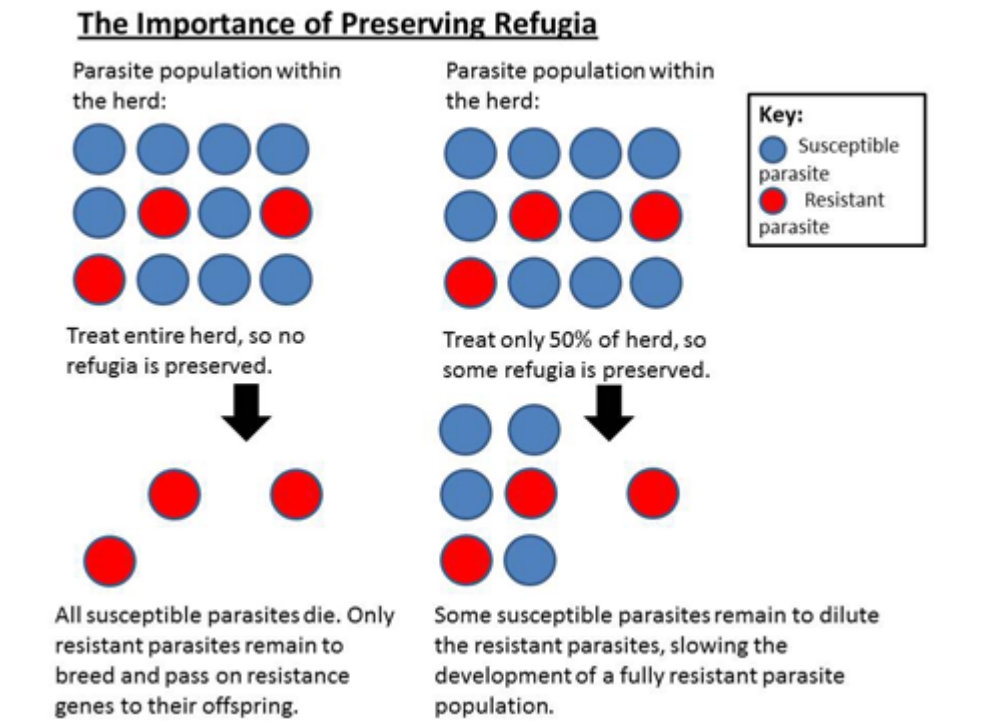
time, parasites are exposed to gradually decreasing drug levels, which may accelerate the development of resistance.

## Refugia

### What is refugia?

Refugia is the proportion of the total parasite population that isn't 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 occurs both inside the animal and in the environment 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; and
- Life stages of the parasite that are unaffected by drug treatment, such as some larval stages.



Note: This graphic wasn't presented at the public meeting and is included here for illustration purposes only.

### What is the purpose of preserving refugia?

The purpose of preserving refugia is to *maintain 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.

### **What are two strategies to preserve refugia?**

Two strategies to preserve refugia are to:

- Leave some animals untreated by limiting treatment to the few animals shedding the most eggs and/or the ones most clinically affected; and
- Deworm when there are more eggs and larvae on the pasture (when environmental refugia is greater). This is the opposite of strategic deworming where treatment is done when environmental refugia is minimal.

Two ways to leave some animals untreated are to:

- Use targeted selective treatments. Use a highly effective drug and treat only those animals that need treatment, based on the results of [fecal egg count reduction tests](#) or FAMACHA© eye color chart scores. [FAMACHA© is an on-the-farm test used only in small ruminants to evaluate an animal's load of *Haemonchus contortus* (barber pole worm) based on the color of the lower eyelid which correlates to the degree of anemia.] Consider the 80-20 rule: 80 percent of parasite eggs are shed by 20 percent of the animals in a flock or herd.
- Focus treatment on certain classes of animals. It may be easier to convince producers to not treat certain classes of animals, rather than convince them to not treat a proportion of each class.

Certain classes of animals may require treatment with antiparasitic drugs more than others. Allowing some animals, depending on their age and class, to have some parasites isn't contrary to production goals. Animals don't have to be completely parasite-free to be healthy and thrive. However, any animal showing clinical signs of parasitism should be treated.

- Low priority classes: Suckling animals, mature horses, and mature lactating dairy cows. These groups of animals can generally be left untreated and still remain healthy due to either (1) their physiologic status (for example, suckling animals that aren't grazing yet, and therefore, are less likely to ingest parasite larvae from the pasture, or adult animals with innate immunity and low parasite exposure); or (2) good pasture management practices.
- Moderate priority classes: Breeding males, first-calf heifers, and mature ewes and does. These groups of animals are maintained in ways that may or may not present risks for parasite transmission. Whether to treat with an antiparasitic drug or not depends more on the specific parasite situation on the farm.
- High priority classes: Replacement heifers, feedlot cattle, grazing sheep and goats, and juvenile horses. Because most animals in these groups are young or on pasture, they are at greatest risk for parasitism and likely require treatment with antiparasitic drugs.

However, young animals should have sufficient parasite exposure to acquire adequate immunity, requiring a balance between exposing them to parasites and deworming them to prevent clinical parasitism. Primarily, veterinarians and producers should not over-treat young animals with antiparasitic drugs.

### **What are the effects of drug formulation on preserving refugia?**

Drug formulation (primarily whether the drug is short- or long-acting) dictates which type of refugia—host-based or environmental—should be maximized. Because short-acting drugs are quickly metabolized, both host-based and environmental refugia can be easily manipulated. Targeted selective treatment will maximize host-based refugia, and treating only during periods of high egg shedding will maximize environmental refugia.

If repeat treatments with a short-acting drug are needed, space the treatments 28 to 30 days apart to help preserve refugia. This gives time for some susceptible parasites to go through one life cycle and re-establish in the host animal. When shed onto the pasture, eggs from these susceptible parasites will dilute the eggs from resistant parasites.

Long-acting drugs make preserving refugia more difficult, as these drugs are slowly metabolized. Environmental refugia is minimally effective. Although larvae already on the pasture aren't exposed to the antiparasitic drug at the time the animals are treated, they become exposed after being ingested by treated animals, even long after initial treatment, because the drug persists in the animals' bodies. For long-acting drugs, it's best to maximize host-based refugia by using targeted selective treatment to leave some animals untreated.

### **Combination Products**

Note: While the following points can apply to combination products in general, the discussion at the public meeting focused on combination products that contain antiparasitic drugs with highly or completely overlapping indications.

#### **What are potential benefits of a combination product that contains two or more antiparasitic drugs with highly or completely overlapping indications?**

Potential benefits of a combination product that contains two or more antiparasitic drugs with highly or completely overlapping indications include:

- Increased spectrum of activity (for combination products with indications that don't completely overlap).

Putting two or more antiparasitic drugs together in a combination product may result in an increased spectrum of activity compared to using the single-ingredient drugs separately. This is helpful in cases where broad-spectrum activity is preferred, such as when diagnostics aren't done to determine which parasite species are infecting the animal. Also, different parasites in different geographic locations develop resistance at different rates. Veterinarians and producers often manage both susceptible and resistant parasites at the same



time on the same farm. Even if one parasite species develops resistance, a broad-spectrum combination product may still have activity against other parasite species present.

Additionally, broad-spectrum combination products may be cheaper for producers than narrow-spectrum single-ingredient antiparasitic drugs. Producers often need to do costly diagnostics to use a narrow-spectrum drug properly because they have to know exactly which parasites are present on their farm to ensure that the drug is effective against those parasites.

- Increased effectiveness.

When appropriately chosen, the component drugs may have an additive or synergistic pharmacologic effect which increases the overall effectiveness of the combination product. Also, parasites may be resistant to one component drug but susceptible to the other, so the combination product is still effective in the face of some resistance.

- Greater convenience.

A combination product is more convenient for producers because they have to administer only one product, instead of giving two or more single-ingredient antiparasitic drugs separately. Combination products also improve animal welfare because producers spend less time handling animals for drug administration.

- A delay in the development of resistance.

According to Dr. Leathwick, modeling and empirical studies have shown that antiparasitic resistance can be delayed when two or more antiparasitic drugs are combined in the same product. Dr. Gasbarre agreed, stating, “[Combination products are the] logical way to approach [the] control of resistance.”

Delaying the development of antiparasitic resistance is particularly important for a new antiparasitic drug that contains a novel active ingredient. Dr. Pritchard stated that combining a new antiparasitic drug with an older, still effective antiparasitic drug will protect the new drug’s effectiveness.

In many cases, combination products slow resistance because fewer resistant parasites survive treatment than with a single-ingredient antiparasitic drug. Therefore, the number of resistant parasites left behind to pass on resistance genes to their offspring is reduced.

The speakers agreed that effective combination products should be used as early as possible, *before* resistance occurs. Particularly for cattle in the U.S., *right now* is the ideal time to start using these products.

### **What would be the expected benefits of an FDA-approved combination product with highly or completely overlapping indications?**

Currently, the only FDA-approved antiparasitic combination products have non-overlapping indications. If, in the future, FDA were to approve an antiparasitic

combination product with highly or completely overlapping indications, veterinarians and producers could expect several benefits from the approved product; mainly, it would meet the agency's strict standards for safety, effectiveness, and quality. Also, during the approval process for a combination product, FDA would confirm the proper dose, establish the safety profile for the drugs in combination, and set the withdrawal period.

FDA and the drug company pursuing approval of the combination product would work together to determine:

- If the component drugs work additively, synergistically, antagonistically, or if they don't influence each other at all; and
- How each component drug interacts with a specific parasite species once the drugs are combined.

The goal of this thorough evaluation is to prevent antagonistic drugs from being combined.

An added benefit of having an FDA-approved antiparasitic combination product with highly or completely overlapping indications on the market in the future is that producers won't need to create their own drug combinations that may be unsafe, ineffective, and/or result in violative tissue residues.

### **What factors make for an ideal combination product?**

Factors that make for an ideal combination product include:

- Resistance mechanisms to the component drugs are controlled by different genes. If the resistance mechanisms are unknown, which is often the case for newer antiparasitic drugs, the combination product should contain component drugs that act on different biochemical receptors in the parasite. If the resistance mechanisms and receptors are unknown, it's best to combine drugs from different classes.
- Resistance mechanisms are homozygous recessive. For offspring to inherit a homozygous recessive resistance mechanism, genetic mutations must occur in both parasite parents, and each must pass on one recessive copy of the resistance gene.
- The level of resistance to each component drug is low or non-existent. Models show that the lower the level of resistance to each component drug, the longer the combination product will be effective. Even in the face of resistance, a combination product may remain effective longer than the component drugs used separately.
- Some [refugia](#) exists at the time of treatment. Combination products work best *with* refugia. The critical concept is to dilute the resistance genes as much as possible. The need to preserve refugia increases when resistance to one or more of the component drugs already exists. With high levels of resistance, more refugia is needed to preserve the effectiveness of the combination product. With low levels of resistance or if the combination product is highly effective, less refugia is needed.

- The component drugs don't negatively interact with each other. *In vivo* interactions of the component drugs may be additive, synergistic, antagonistic, or indifferent. If the component drugs work antagonistically, then the effectiveness of the combination product is reduced, or a toxicosis may result in the host animal.

An example of antagonistic interactions was seen when albendazole, levamisole, and ivermectin were combined. The combination product resulted in lower albendazole and higher ivermectin systemic exposure levels as compared to the exposure level for each drug separately. The level of levamisole systemic exposure was unchanged in the combination product.

Antagonistic interactions, such as the one in the above example, illustrate the importance of choosing the right drugs to combine and putting them in the right formulation. Showing that the combination product is safe and effective is also critical.

- The component drugs have similar half-lives and time-to-kill curves, so they're in the animal's body at sufficient concentrations during the same time frame. This maximizes the combination product's effectiveness at killing the parasites and at reducing the number of resistant parasites that survive treatment. If the half-lives and time-to-kill curves are quite different, one component drug may be present and the other absent at a given time. This situation allows some parasites that are resistant to one component drug to survive treatment, thereby increasing the proportion of resistant parasites.

### **What are some concerns about a combination product?**

Some concerns about a combination product are:

- Producers may use it inappropriately, such as administering an incorrect dose, giving it too frequently, or using it in an off-label (extra-label) manner without involving their veterinarian. However, such inappropriate use is just as likely with single-ingredient antiparasitic drugs.
- A combination product may promote multi-drug resistance. If the component antiparasitic drugs act on the same parasite gene or share a common resistance mechanism, then combining these drugs will impose an even higher selection pressure, possibly resulting in multi-drug resistance. However, multi-drug resistance is less likely to develop if the factors that make for an ideal combination product are present.

### **Over-the-Counter or Prescription-Only?**

#### **Should antiparasitic drugs be prescription-only?**

The use of over-the-counter (OTC) antiparasitic drugs without veterinary oversight has contributed to the development of antiparasitic resistance. When veterinarians are involved in parasite management, they can use their knowledge of the behavior and biology of both the host species and the parasites to help producers implement

effective parasite control programs that help slow resistance. Also, veterinarians' experience with diagnostics to detect and monitor antiparasitic resistance leads to more appropriate use of antiparasitic drugs.

Because the use of OTC drugs doesn't require a veterinarian-client-patient relationship, veterinarians have fewer opportunities to interact with producers and help them make decisions about parasite management. Producers can buy an OTC antiparasitic drug without a prescription, so veterinarians generally don't have a "vested financial interest...in developing any kind of expertise in parasite control because they are not charging for the service and they are not selling the drugs," stated Dr. Reinemeyer.

### *The Denmark Model*

The effects of making antiparasitic drugs prescription-only can be seen in Denmark. In 1999, Denmark passed legislation making antiparasitic drugs for livestock prescription only and banning prophylactic use of these drugs.

In the Denmark model, veterinarians play a critical part in parasite control. The legislation requires a veterinarian's diagnosis before an antiparasitic drug can be prescribed, and farmers can only get the drug through veterinarians. Farmers must also receive training on how to detect and manage antiparasitic resistance before they can give an antiparasitic drug to their animals. Sweden, Finland, and the Netherlands recently enacted similar legislation.

In horses<sup>1</sup> in Denmark, the 1999 legislation has resulted in:

- Less frequent dewormings;
- More regular (about twice yearly) fecal egg counts;
- Veterinarians becoming more involved in parasite control; and
- Owners becoming more educated about parasites and parasite control.

### *Concerns about the Denmark Model*

One concern about the Denmark model is that the traditional fecal examination method, the [fecal egg count](#), doesn't detect all parasites in all animals due to its limited sensitivity. This may cause a veterinarian to incorrectly assess an animal's parasite burden, potentially resulting in less effective treatment. Better diagnostics need to be developed to overcome the limitations of the fecal egg count before legislation similar to the Denmark model is adopted more globally.

Another concern is the potential for highly pathogenic parasites to re-emerge due to treating too infrequently. For example, *Strongylus vulgaris* (large strongyle or bloodworm) is now rare in most horse populations. But if horses aren't dewormed often enough, equine populations may see a resurgence of these parasites due to

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<sup>1</sup> In Denmark, the term "livestock" includes horses. In the U.S., horses are considered companion animals, not livestock.

unique aspects of the parasites' biology, specifically their long lifecycle compared to other equine parasites.

## Fecal Egg Counts and Fecal Egg Count Reduction Tests

### What are some key points about fecal egg counts and fecal egg count reduction tests?

The fecal egg count (FEC) is the traditional method to count parasite eggs in a fecal sample. The fecal egg count reduction test (FECRT) is a mathematical calculation of the reduction in parasite eggs from the pre-treatment FEC to the post-treatment FEC.

It's important to note that some parasite species can't be differentiated by microscopically examining their eggs in a fecal sample. For example, most strongyle parasite eggs look identical microscopically, so they can't be differentiated from each other. In another example, species in the *Nematodirus* genus can be differentiated by looking at their eggs under a microscope, but species in both the *Haemonchus* and *Teladorsagia* genera cannot be differentiated that way.

Dr. Kaplan considers the FECRT to be the "practical gold standard" for on-the-farm diagnosis of antiparasitic resistance. Although the FECRT is a coarse method to measure resistance, arguably more qualitative than quantitative, it's still a predictable diagnostic tool.

More veterinarians are using the FECRT to monitor antiparasitic resistance and tailor the parasite control program to the needs of the farm, but unfortunately, the percentage of veterinarians who use the test is still small. Ideally, veterinarians should perform a FECRT along with other diagnostics, such as coproculture or larval development assays, to figure out the most appropriate antiparasitic drug for a farm.

To have confidence in the results, veterinarians need to perform the FECRT in a standardized way. The [World Association for the Advancement of Veterinary Parasitology](#) issued standardized guidelines for performing the test in small ruminants, but not in horses or cattle yet. The methods for horses and cattle are inconsistent largely because of veterinarians' personal preferences and experiences. For example, veterinarians differ in how long they wait to collect the second fecal sample after treatment and in how they calculate group means. There are also host-specific biological differences, such as:

- In horses, pre-treatment fecal egg counts differ greatly between animals. Some horses may have low, even negative, pre-treatment fecal egg counts.
- In cattle, fecal egg counts tend to decrease as animals get older, and the values also fluctuate seasonally.

User inconsistencies and biological differences create challenges in interpreting a farm's overall results and in comparing results across farms. To reduce variability and improve result consistency, veterinarians need to choose one way to perform a FECRT in horses and cattle. At a minimum, the same method should be used repeatedly on one farm. Despite its limitations, the FECRT is still the best available

field test to monitor antiparasitic resistance and antiparasitic drug effectiveness in these species.

## **Resistance Indications and Study Design**

### **Are resistance indications appropriate?**

FDA labels an approved antiparasitic drug with a specific indication that lists which parasites the drug is effective against. FDA decides which parasites to include in the indication based on the results of effectiveness studies conducted by the drug company during the approval process.

At this time, FDA doesn't label an antiparasitic drug with a "resistance indication," meaning the agency doesn't allow parasites known to be resistant to a certain drug or drug class to be included in the indication. For example, FDA currently doesn't allow ivermectin-resistant *Haemonchus* species to be included in the indication for a non-ivermectin drug.

However, current thinking suggests that resistance indications may be appropriate for three types of antiparasitic drugs:

- A new broad-spectrum drug with a novel mechanism of action.
- A new narrow-spectrum drug that selectively targets resistant parasites (for example, a drug that targets resistant *Cooperia* species). To use a drug in a targeted way, it's best to diagnose the parasites to the species level, but these diagnostics aren't readily available now.
- A [combination product](#) that contains two highly effective component drugs, so that the combination product is nearly 100 percent effective against all parasite species listed in the indication.

Based on data from statistical studies with computer models as well as from Australia and New Zealand (both countries have some antiparasitic drugs labeled with resistance indications), it appears that antiparasitic drugs developed to target resistant parasites don't speed up the further development of resistance. As resistance continues to emerge and limit the choices of effective antiparasitic drugs, it may be prudent to recommend, perhaps require, diagnostics to be done to monitor antiparasitic resistance and to support the use of a drug targeted for resistant parasites.

### **How should effectiveness studies be designed for a drug targeted for resistant parasites?**

DISCLAIMER: This section is intended solely as an overview of the scientific discussion regarding the design of effectiveness studies for a drug targeted for resistant parasites. The information represents the opinions of the outside experts who presented at the public meeting and should not be interpreted as either recommendations to FDA or FDA guidance.

### *Characterize and Identify Isolates*

In studies to evaluate the effectiveness of an antiparasitic drug targeted for resistant parasites, isolates of a resistant strain of the parasite species should be characterized by the extent of their resistance and cross resistance. The extent of resistance indicates an isolate's level of resistance (low or high) to a particular antiparasitic drug. Cross resistance means resistance of an isolate to more than one drug class. Isolates should also be characterized by genotype and phenotype, and genotype should be correlated with phenotype.

A challenge to characterizing isolates is that one isolate is not representative of all resistant isolates. For example, a *Cooperia punctata* isolate resistant to ivermectin is not representative of all ivermectin-resistant *Cooperia punctata* isolates. Besides resistance differences, other biological differences, such as pre-patent period and immunogenicity, should be considered when characterizing resistant isolates. Also, more research is needed to develop better assays to survey parasite populations, such as *ex vivo* assays to identify resistant isolates based on genotype or phenotype or to confirm clinical cases of resistance.

Identifying isolates to the species level (to "speciate" them) can be difficult. For example, as mentioned in the [FEC and FECRT section above](#), the eggs of most strongyle species look alike. Fecal examination methods that count only eggs, such as the FEC, can detect the presence of strongyle parasites but not differentiate which species are present. The only way to speciate the majority of strongyles is by examining the actual worms, by either performing a parasite count (see below) or coproculture (a test that involves culturing parasite eggs from a fecal sample and identifying hatched larvae to the species level).

Parasite counts are the current standard for isolate identification. In this method, parasites—adults and larvae, not eggs—are directly counted and identified to the species level under a microscope. These tests are expensive, labor-intensive, and raise ethical concerns because the host animals must be euthanized for necropsy.

While molecular methods for species identification show promise, they aren't fully developed for all parasites. The only good molecular test currently available is one that identifies certain benzimidazole-resistant isolates to the species level in small ruminants and horses. The main reason for this test's success is that the molecular mechanisms for benzimidazole resistance are well understood.

Characterizing and identifying resistant isolates are critical steps in the study design. It's also critical that drug companies have access to these resistant isolates for use in studies. For consistency, the same resistant isolates should be used in multiple studies—both in effectiveness studies and in studies to evaluate resistance mechanisms.

### *Define and Measure Resistance*

How resistance is defined in a study depends on what method is used to measure it. If a 99 percent reduction in susceptible isolates is expected, then anything less is resistance. It's difficult to prove resistance starts at less than 99 percent if there's a small sample size and the method has a high level of variability. (For example, the FECRT has a high level of variability due to fluctuation in egg shedding and other host-parasite interactions.) Defining resistance and selecting a method to measure it

come down to statistics. The method's precision depends on the number of animals and variables in the study.

#### *Determine Effectiveness*

When evaluating a new antiparasitic drug's effectiveness against resistant parasites, it needs to be shown that resistance to an older, already approved antiparasitic drug exists. To do this, data from when the older antiparasitic drug was approved could be compared with new data on that same drug. For example, if the data from the original approval established an effectiveness of 95 percent and a recent parasite count study showed a statistically significant decrease in the drug's effectiveness to 90 percent, then resistance may be determined to exist based on these numbers.

The next step is to select an appropriate effectiveness threshold to use in studies with the new antiparasitic drug. For example, the effectiveness threshold may need to be increased from 95 percent to 98 percent to help ensure longer effectiveness of the new drug after it is marketed.

## **Transdermal (Pour-On) Antiparasitic Drugs**

### **What is the role of transdermal (pour-on) antiparasitic drugs in the development of resistance?**

Accumulating and compelling evidence shows that transdermal (pour-on) antiparasitic drugs aren't as effective in the field as oral or injectable antiparasitic drugs, and that the use of these drugs speeds up the development of resistance.

Of the three routes of administration for antiparasitic drugs—oral, injectable, and transdermal—transdermal is the least recommended and the least accurate. When given transdermal antiparasitic drugs, animals are often exposed to sub-therapeutic drug levels because of under-dosing due to:

- Improper administration. Producers and even veterinarians often don't follow the directions on the label. With few exceptions, transdermal drugs are correctly applied only in clinical studies.
- Variable transdermal absorption rates and variable effectiveness, due to the skin "acting like a raincoat." Pharmacokinetic studies with some transdermal drugs show that the absorbed drug levels are so low, it's hard to see how they work at all.
- Licking. Animals often lick the transdermal drug off their skin before it can be absorbed. Depending on the drug's pharmacology, this may increase the animals' drug exposure due to some oral absorption in addition to transdermal absorption. Conversely, other animals licking the drug off treated animals may result in under-dosing, as this decreases drug exposure.

A 2007 to 2008 survey of beef cow-calf health done by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service showed one-third of participating farms had less than 80 percent reduction in fecal egg counts. A large majority of farms with these results had used a transdermal macrocyclic lactone.



## Role of Education

### What is the role of education in slowing down antiparasitic resistance?

Veterinarians seem poorly informed about the current level of antiparasitic resistance in the U.S., particularly in cattle. While veterinarians and producers agree that antiparasitic resistance is a problem, they, in general, still mistakenly believe that reducing treatment frequency causes negative economic and animal health consequences. They need to be shown the financial consequences of antiparasitic resistance. The economic loss from decreased production due to antiparasitic resistance may, over time, cost more than the overhead to run a FECRT or other diagnostics.

In the U.S., the equine industry and small ruminant producers are more progressively tackling antiparasitic resistance compared to the cattle industry. Equine veterinarians are abandoning traditional approaches to parasite control, such as strategic deworming and scheduled rotational deworming programs. Instead, they're adopting new methods of parasite control, such as using the FECRT and other diagnostics to make more informed treatment decisions and educating clients on better pasture management practices.

The [American Consortium for Small Ruminant Parasite Control](#) developed training programs for veterinarians and producers on FAMACHA©. Feedback from these programs indicated that 73 percent of producers treated their animals less often, and 88 percent reported they saved money in the first year after training.

But there's been little change among cattle veterinarians, partly because short-term maximal productivity is still the driving force to antiparasitic drug use in cattle.

Antiparasitic resistance is inevitable, but its development can be slowed and its extent limited. Australia and New Zealand struggle with severe antiparasitic resistance in sheep, which greatly affects each country's agricultural economy. To address the issue, both countries developed large-scale research and extension programs as well as awareness campaigns aimed at training veterinarians and sheep producers on using FAMACHA© and preserving refugia. As a result, Australia and New Zealand have had success at slowing down antiparasitic resistance in sheep, especially on well-managed farms.

Changing the historic pattern of antiparasitic drug use requires a dramatic paradigm shift and extensive re-education of veterinarians and producers, as well as better education of veterinary students. Large animal parasitology classes at many veterinary schools often teach students outdated information. And unfortunately, veterinary parasitologists don't have the resources or infrastructure to appropriately educate, or re-educate, veterinarians and producers about antiparasitic resistance and appropriate antiparasitic drug use. But the drug companies that develop and manufacturer these drugs could, and should, embrace this stewardship. It may be helpful if drug companies combined the approval of new antiparasitic drugs with educational programs to reinforce appropriate use.

The current situation with antiparasitic resistance in the U.S. is similar to where Australia and New Zealand were 15 to 20 years ago. The U.S. should acknowledge that antiparasitic resistance is emerging, and by learning from the experiences of other parts of the world, pro-actively approach the issue.

## **Conclusion**

### **Know More, Do More**

FDA's public meeting on antiparasitic drug use and resistance in ruminants and equines successfully opened the lines of communication between the agency, veterinary parasitologists, veterinary pharmacologists, and the public. The knowledge shared and gained will help FDA and the veterinary community move forward together to combat antiparasitic resistance in the U.S.