Antiparasitic resistance, specifically resistance to anthelmintics among gastrointestinal parasites of cattle, small ruminants, and horses, is both a health and a welfare issue for US grazing livestock and potentially threatens animal agricultural production. The veterinary community broadly accepts that antiparasitic resistance is widespread among small ruminant parasites, particularly in Australia, New Zealand, South Africa, and some South American countries. And, many veterinarians and livestock producers acknowledge that antiparasitic resistance is also a problem among small ruminant parasites in the United States. However, awareness of antiparasitic resistance in cattle and horse parasites in the United States and other countries is relatively low, even while reports of resistance involving parasites of these species are increasing. Although the FDA Center for Veterinary Medicine (CVM) determines whether antiparasitic drugs for animals are safe and effective before approval, the drugs’ continued effectiveness after approval largely depends on how they are used by veterinarians and producers.

As a consequence of sole reliance on the use of antiparasitic drugs for parasite control and other unsustainable management practices, such as treating entire herds on the basis of set protocols instead of actual need, widespread resistance to all major families of broad-spectrum anthelmintics may develop in the near future. To help combat this threat, the CVM has developed an outreach initiative to educate veterinarians and livestock producers on how to integrate selective antiparasitic drug use with sustainable management practices. The goal is to maintain the effectiveness of current antiparasitic drugs for as long as possible. As part of this initiative, the CVM has been collaborating with other regulatory agencies, veterinary professional organizations, livestock producer groups, the animal drug industry, researchers, and educators on efforts to slow the development of resistance among parasites affecting US grazing livestock.

Background

The first macrocyclic lactone, ivermectin, came onto the US veterinary market in 1984 and dramatically changed how veterinarians and livestock producers treated and controlled gastrointestinal parasites in grazing livestock. Because of their wide spectrums of activity and long half-lives, macrocyclic lactones had high levels of effectiveness when first introduced. They were also easy to administer, inexpensive, and conveniently available over the counter. For all these reasons, parasite control programs for cattle, sheep, goats, and horses relied primarily, and sometimes exclusively, on the use of macrocyclic lactones to eradicate parasites. Other management practices, such as controlling pasture usage, selectively treating certain animals, and performing diagnostic procedures to determine the parasite load, were largely ignored. Instead, entire herds were treated simultaneously, usually at strategic times when most parasite life stages were inside the animals versus on the pasture. This treatment practice, which is still common today, results in an almost 100% parasite kill rate. Although ideal in the short-term, complete removal of susceptible parasites leaves behind only those that are resistant to the given antiparasitic drug. This leads, in the long-term, to a population of drug-resistant parasites on the farm and decreased effectiveness of the drug.

The first report of nematode resistance to ivermectin was published in 1988 and involved sheep raised in South Africa. Since then, resistance to macrocyclic lactones has been documented worldwide in parasites of small ruminants, horses, and cattle.

Antiparasitic resistance is an emerging health crisis for US grazing livestock, and to address it, veterinarians and livestock producers, particularly in the cattle industry, need to shift their views on parasite control from a goal of parasite elimination to one of parasite management. Recent scientific evidence shows that eliminating 100% of parasites from a herd or farm is not sustainable owing to the inevitable development of antiparasitic resistance. A more sustainable parasite control program uses management tools to reduce parasite loads within herds while maintaining a low, but not zero, level of drug-susceptible parasites. Combining the concept of refugia—whereby a proportion of the total parasite population is left unexposed to drug treatment by not treating all animals at the same time with an antiparasitic drug—with other good management practices can increase the time antiparasitic drugs remain effective.

When examining how and why antiparasitic resistance develops, it is inappropriate to consider cattle, small ruminants, and horses as the same. The varied
Role of the CVM

The Federal Food, Drug, and Cosmetic Act, which Congress passed in 1938 and later amended in 1968 with the Animal Drug Amendments, gives the FDA the authority to regulate animal drugs. Under this federal law, the FDA ensures that animal drugs are safe and effective for their intended uses and that they do not result in unsafe residues in foods.10

The mission of the FDA CVM is to protect human and animal health. As part of this mission, the CVM is responsible for reviewing animal drugs for approval under the Food, Drug, and Cosmetic Act. Before approving an animal drug, the center evaluates its safety on multiple levels: safety in the species for which the drug is intended, safety for people who will handle and administer the drug to animals, and safety of food products derived from treated food-producing animals. The CVM also reviews the effectiveness of the drug; ensures the manufacturing process is adequate to preserve the drug's identity, strength, quality, and purity; and ensures the drug is properly labeled. In addition, the National Environmental Policy Act requires the CVM to consider the environmental impact of the center's decision to approve the drug. The goal of this review process is to have safe, effective, reliable, and properly labeled animal drugs available to veterinarians and animal owners.

The CVM's challenge is incorporating current science into the regulatory framework for evaluating animal drugs. Emerging science indicates that resistance is developing to antiparasitic drugs that were effective at the time of approval. However, the issue of antiparasitic resistance is not clear-cut. A parasite population on one farm may have considerable resistance to a particular antiparasitic drug, yet the same drug may be effective against parasites on a neighboring farm. Biology of the host animal, genetics of the parasite, how the antiparasitic drug is used, and the drug's pharmacological characteristics all contribute to whether and how quickly antiparasitic resistance will develop. In the face of this multifactorial problem, the long-term effectiveness of antiparasitic drugs is questionable.

On March 5 and 6, 2012, the CVM held a public meeting titled, “Antiparasitic Drug Use and Resistance in Ruminants and Equines.” At the meeting, the CVM hosted seven internationally recognized experts in veterinary parasitology and pharmacology. These experts discussed the current state of antiparasitic resistance in the United States and worldwide, how to identify and define antiparasitic resistance, and ways antiparasitic drugs can be used, alone or in combination, in ruminants and equids to maximize drug effectiveness and minimize development of antiparasitic resistance. Members of the public were invited to attend the meeting and were able to speak during two open comment periods.

The public meeting was the CVM’s first major step in acknowledging antiparasitic resistance among parasites of US grazing livestock. The transcript from the two-day meeting, Federal Register notice, and presentation slides are available on the CVM website (www.fda.gov/AnimalVeterinary/ResourcesForYou/ucm318015.htm).

Antiparasitic Resistance Management Strategy

The CVM gleaned a wealth of information from the public meeting, including the fact that there is a need for further education on antiparasitic resistance. In response, the CVM developed the Antiparasitic Resistance Management Strategy (ARMS). This initiative promotes selective use of antiparasitic drugs together with sustainable management practices to maintain the effectiveness of antiparasitic drugs in grazing livestock species. Currently, the ARMS focuses on gastrointestinal parasites in cattle, small ruminants, and horses; the initiative does not encompass parasites of swine, poultry, fish, dogs, or cats at this time.

Started in September 2012, the ARMS takes a three-pronged approach: education, research, and regulation. Educating veterinarians and livestock producers is the best way the CVM can influence the paradigm shift from parasite elimination to parasite management. To this end, the group at CVM heading the ARMS initiative has written a pamphlet titled, “Helpful Information for Veterinarians: Antiparasitic Resistance in Cattle and Small Ruminants in the United States,” which can be downloaded from both the CVM (www.fda.gov/downloads/AnimalVeterinary/ResourcesForYou/UCM347442.pdf) and AVMA (ebusiness.avma.org/EBusiness50/ProductCatalog/ProductCategory.aspx?ID=138) websites. The CVM website also includes a page dedicated to antiparasitic resistance (www.fda.gov/animalveterinary/safetyhealth/ucm350360.htm).

The ARMS group has reached out to many organizations to increase awareness of both the initiative and antiparasitic resistance in general. Members have spoken to domestic and international groups, including professional veterinary and agricultural organizations as well as government agencies. These talks emphasize not only the science behind antiparasitic resistance, but also the collaboration between the CVM and other organizations. One way professional veterinary organizations, such as the AVMA and practitioner associations (eg, the American Association of Equine Practitioners, American Association of Bovine Practitioners, and American Association of Small Ruminant Practitioners) can help raise awareness of antiparasitic resistance is by offering more continuing education dedicated to this topic at their conferences.

From discussions with international regulators, the ARMS group has gained insight into how other countries are currently dealing with antiparasitic resistance and how they have responded to the problem in the past. By learning from other countries’ experiences, the CVM can hopefully avoid unnecessary or redundant actions when addressing antiparasitic resistance, particularly from a regulatory standpoint.
Speakers at the 2012 public meeting stated that more research is needed in areas such as elucidating the mechanisms of parasite resistance against antiparasitic drugs; understanding the heredity of parasite resistance; determining methods to validate and standardize diagnostic procedures, such as the fecal egg count reduction test in cattle and horses; and developing more user-friendly diagnostic tests to identify and quantify antiparasitic resistance on farms. Unfortunately, limited funding is a common obstacle to researching antiparasitic resistance.

Within the federal government, the USDA Agricultural Research Service is conducting some research on livestock parasites and antiparasitic resistance. Hopefully, research opportunities can be expanded in the future at both the USDA Agricultural Research Service and the CVM Office of Research.

Because the initiative originated within the CVM, the ARMS group’s greatest direct influence has, arguably, been in the regulatory realm and, specifically, in the area of developing improved, science-based policies to guide the approval process for new anthelmintics. Current science has already changed some of the CVM’s regulatory policies. For example, because of evidence presented at the 2012 public meeting on how carefully selected combinations of anthelmintics with highly or completely overlapping indications can slow the development of antiparasitic resistance when used with sustainable parasite management practices, the CVM is now open to drug companies proposing such combination products for approval.

**Conclusion**

Science shows that the development of antiparasitic resistance cannot be stopped. When exposed to a drug designed to kill them, preadapted resistant parasites will propagate and pass on resistance genes to their offspring and thus the parasite population will evolve and develop resistance. However, this natural process can be slowed when veterinarians and livestock producers selectively use antiparasitic drugs along with sustainable parasite management practices, the CVM is now open to drug companies proposing such combination products for approval.

The ambitious goal of maintaining long-term effectiveness of antiparasitic drugs used in US grazing livestock species cannot be attained by the CVM alone, nor should it be. Rather, veterinary professional organizations, the agricultural industry, academic institutions, and the animal drug industry should all be involved in educating veterinarians and livestock producers about selective antiparasitic drug use and sustainable parasite management practices. It will take the combined effort of all these groups to shift the paradigm and slow the development of antiparasitic resistance. Hopefully, it will soon be the norm, not the exception, for veterinarians and producers to work as partners to develop sustainable parasite management programs specific to individual farms.

**References**


For all commentaries, views expressed are those of the authors and do not necessarily reflect the official policy of the AVMA.