# *Thanks to Raccoon Valley Pony Club*

# The Horse: Drugs for the Deworming War

**How Do They Work?**

All nematocides (drugs that kill nematode or roundworm parasites) essentially kill worms by either starving them to death or paralyzing them. Because worms have no way of storing energy, they must eat almost continuously to meet their metabolic needs. Any disruption in this process results in energy depletion, and interfering with feeding for 24 hours or less is sufficient to kill most adult parasites.

Parasites will also die if they become paralyzed and temporarily lose their ability to maintain their position in the gut.

Although dewormers are sold under many brand names, there are really only nine distinct compounds currently approved for use against equine parasites (see "Dewormers Available in the United States" on page 66). These nine drugs belong to only five different chemical classes. Because all drugs in a chemical class kill worms by the same mechanism, we'll use a chemical classification system to discuss each dewormer in greater detail. For a translation to the more familiar brand name, see the table.

**Benzimidazoles**

Benzimidazoles interfere with a worm's energy metabolism on a cellular level. They bind to a specific building block called beta tubulin and prevent its incorporation into certain cellular structures called microtubules, which are essential for energy metabolism. This is analogous to treating bricks so they won't bind to mortar; walls constructed with such materials would be unstable and ultimately collapse.

Interfering with energy metabolism is a much more basic mode of activity than those of the other classes of dewormers. For this reason, the benzimidazoles are also able to kill nematode eggs, a property not shared by other classes of dewormers.

Benzimidazoles are available in granules, paste, and suspension formulations. As a group, they're more effective when given several days in a row. This property has been exploited in the Panacur PowerPac, which has a five-day treatment regimen for efficacy against migrating large strongyle larvae and encysted cyathostomes.

**Tetrahydropyrimidines**

The tetrahydropyrimidines (pyrantel pamoate and pyrantel tartrate) mimic the activity of acetylcholine, a naturally occurring neurotransmitter that initiates muscular contraction. The action of acetylcholine on nerve cells is usually brief and temporary because it is degraded by a specific enzyme known as acetylcholinesterase. Pyrantel salts induce the same muscle-contracting effect as acetylcholine, but the resulting contraction is irreversible. This results in rigid paralysis, so the worm is unable to feed and quickly starves. Pyrantel has the fastest activity of any of the major deworming classes used in horses, but worm populations tend to bounce back quickly from it--strongylid fecal egg counts are suppressed for only about four weeks. Also, pyrantel salts only affect adult parasites--they don't hurt the larval stages.

Pyrantel pamoate is available in suspension and paste formulations, while pyrantel tartrate is formulated in alfalfa pellets and can be fed daily at 1.2 mg/pound daily for prevention of strongyles and ascarids, or used at a higher dosage as a single treatment to remove existing worms.

**Heterocyclic Compounds**

Several dewormers are classified as heterocyclic compounds, but piperazine is the only one used in horses. Piperazine works by depolarizing muscular membranes, which renders them resistant to the action of acetylcholine. Worms affected by piperazine are paralyzed and cannot feed properly. The action of piperazine is limited to adult parasites, so it is likely that fecal egg counts would remain low for only a limited time following treatment with this drug.

Although it was popular a few decades ago, today piperazine is used infrequently in horses. It is available as a liquid or powder formulation, and it must be administered in voluminous doses that usually require nasogastric intubation. There is also a pelleted form that can be fed as a supplement.

**Macrocyclic Lactones**

The macrocyclic lactones act on very specific sites in nematode nerve and muscle cells, disturbing the normal transmission of nervous stimuli to muscles. The result is flaccid paralysis, with an inability to feed or swallow nutrients. Macrocyclic lactones are the most potent killers of worms, being effective at less than one-tenth the dosage of other classes of dewormers. They also have the unique quality of killing external parasites, such as lice, mites, and the cutaneous (inhabiting the skin) larvae of *Onchocerca, Habronema*, and *Draschia*.

But macrocyclic lactones also have a down side--they don't act as quickly as other deworming drugs. Three to four days is required before strongylid egg counts reach their lowest level post-worming.

Macrocyclic lactones are available in paste or solution formulations (ivermectin) or as an oral gel (moxidectin).

**Isoquinoline-Pyrozines**

Praziquantel is the sole member of the isoquinolone class used in horses. It is also unique in that it has no activity against nematodes (roundworms). Praziquantel is effective only against cestodes, or tapeworms (*Anoplocephala spp.*). It acts by disrupting the integument (the worm's outer layer), which renders the worm incapable of maintaining a balanced equilibrium of body fluids and chemicals. Tapeworms killed by praziquantel look very damaged when they eventually pass out in the feces of a horse.

Praziquantel is currently marketed only in combination with macrocyclic lactones, and the combination formulation is that of the parent compound (ivermectin if paste, moxidectin if a gel).

**Common Ground**

Despite their differences, all anthelmintics for use in horses must be approved by the Center for Veterinary Medicine of the Food and Drug Administration (FDA). Before receiving FDA approval, however, dewormers must undergo rigorous testing to demonstrate that they are safe and effective for the intended uses. FDA guidelines generally require an anthelmintic to remove at least 90% of the target parasites, and they are very strict about the information that appears on the product label.

Nearly all currently marketed equine anthelmintics could be called "broad spectrum," meaning they kill a broad variety of parasites rather than targeting a single species. For horses, broad spectrum means efficacy against large strongyles, cyathostomes (small strongyles), ascarids, and pinworms. Narrow spectrum is anything less.

Over-the-counter anthelmintics do not require refrigeration, but can be damaged by excessive heat. Observe the storage conditions recommended on the packaging, and remember that a truck's dashboard can get darned hot in the summer.

Dewormer labels also include an expiration date, after which the stability and concentration of the product can no longer be guaranteed. Expired drugs are not likely to become toxic, but they might become less effective, and their physical properties might be altered. For instance, if your paste is kept too long it might shrivel into cement.

**Dewormer Myths**

Forty years ago, dewormers were a much different kettle of fish than they are today. More difficult to administer, and with a smaller margin of safety and a narrower spectrum of efficacy than anything available today, those early dewormers should be just a memory. But some of the beliefs that came with them persist; like so many other things in the equine industry, tradition swings a bigger stick than logic.

Let's tackle a few of the more outdated notions head-on.

***Myth #1--***"The only way to ensure my horse gets dewormed properly is to get my veterinarian to tube him."

***False--***Giving an anthelmintic via nasogastric tube is still considered to be the only "guarantee" that all of the drug is ingested. But this practice originated strictly because most early dewormers were either very irritating to oral membranes (like carbon disulfide) or required voluminous doses that could not be delivered in any other way (piperazine and combinations thereof). With the modern compounds and formulations, there is no need to use a nasogastric tube for anthelmintic administration.

***Myth #2--***"Chemicals toxic enough to kill worms must be toxic to my horse, too."

***False--***In the 1960s and 1970s, a drug class known as organophosphates was used in horses to remove bots and various other internal parasites. At therapeutic dosages, organophosphates could cause physiologic changes in horses as well as in worms. Toxic effects in horses included colic, salivation, incoordination, and muscular twitching. There also was some concern about organophosphates causing abortions.

Today's dewormers are vastly superior to the organophosphates we once used. They have broad margins of safety and are administered to millions of horses world-wide without incident. Today, the major safety issue with deworming is ascarid impactions following treatment of foals, weanlings, and yearlings harboring heavy parasite loads, and there are strategies to treat those horses without triggering that cascade. Killing other types of adult worms is essentially without consequence, as is killing most larval stages in the tissues.

***Myth #3--***"Dewormers aren't safe to use in pregnant mares."

***False--***For a drug label to state that the product is safe for use in pregnant mares, the FDA requires the manufacturer to conduct rigorous testing to prove it. With the exception of the three drug combinations that include praziquantel (see "Dewormers Available in the United States" above), all currently marketed anthelmintics are approved for pregnant mares.

The lack of pregnant mare safety claims for the praziquantel combinations is due to their recent entry into the market rather than to any suspected hazards. Because pregnant mare safety testing usually requires a minimum of two years, most pharmaceutical companies will seek initial approval of their drug while waiting on a pregnant mare safety trial. If and when safety is demonstrated, the label can be amended to reflect that fact. In the meantime, the manufacturer is able to sell a product that is not labeled for use in pregnant mares to begin recouping their research and development investment while the patent life is ticking away.

***Myth #4--***"I can get the same deworming effect without using toxic chemicals on my horse by giving him a safe, natural remedy like diatomaceous earth."

***Questionable--***Although many herbal and "natural" products are marketed as being effective against worms, none of them are currently regulated by the Centers for Veterinary Medicine. As a result, they are not subject to the same FDA restrictions regarding label claims.

Also, no scientific evidence supports the efficacy of most herbal dewormers. In the case of diatomaceous earth, which is composed largely of silica (the main component of glass), there is some evidence that it might be abrasive to the integuments of worms in the GI tract, but it can only target those worms in the digestive system and might not be enough to kill them. And, one has to wonder what that same abrasiveness might do to your horse's delicate intestines!

If you choose to try a natural or herbal anthelmintic on your horse, check its efficacy by performing a fecal egg count before and after administration (see "Diagnosis: Examining the Evidence," www.TheHorse.
com/emag.aspx?id=5193, for information on doing a fecal egg count). That will give you some indication as to whether they've provided the protection your horse needs.

***Myth #5--***"To keep worms from developing resistance, I should use a different drug each time I treat my horse."

***False--***Rotation will be addressed more fully in next month's article on anthelmintic resistance. For now, keep in mind that the practice of rotating equine dewormers began four decades ago, and the rationale wasn't resistance, because that was long before anthelmintic resistance became a prevalent problem. Instead, rotation was recommended because earlier anthelmintics didn't have broad-spectrum activity. Owners alternated among various products to cover any holes in the spectra of the other drugs. (For example, phenothiazine didn't kill ascarids, so piperazine was used from time to time. Neither was effective against bots, so that required dichlorvos.)

Because most modern dewormers are "broad spectrum" and strike down many worm species in a single blow, rotation as most of us understand it is now largely a moot practice for horses. There are routines for managing resistance, however, which we'll talk about next month.

**THEHORSE.COM POLL RESULTS**

**Do you deworm your horse...**

* Every three months: 35.04% (328)
* Every six weeks: 31.94% (299)
* Other: 13.57% (157)
* Daily: 9.94% (93)
* Every six months: 8.97% (84)
* Never: 0.53% (5)

**TOTAL VOTES: 936**

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| **DEWORMERS AVAILABLE IN THE U.S.**  |
| **DRUG CLASS** | **GENERIC ANTHELMINTICS** | **BRAND NAMES** |
| Benzimidazoles | Fenbendazole | Panacur; Safeguard; Panacur PowerPac |
| Oxfendazole | Benzelmin |
| Oxibendazole | Anthelcide E.Q. |
| Heterocyclic compounds | Piperazine | Piperazine |
| Macrocyclic lactones | Ivermectin | Zimecterin, Rotation 1, Ivercare, Equell |
| Moxidectin | Quest, Quest Plus, ComboCare |
| Tetrahydropyrimidines | Pyrantel pamoate | Exodus; Pyrantel Pamoate Paste; PSI's suspension; Strongid-T; Strongid Paste |
|   | Pyrantel tartrate | Strongid-C; Strongid-C 2X; Continuex; Continuex 2X |
| Isoquinoline-pyrozines | Praziquantel | Equimax; Quest Plus; Zimecterin Gold |

**MORE DEWORMING OPTIONS: Are Generics Just As Good?**

The first company to develop a drug generally secures a patent that guarantees exclusive rights to manufacture and market the compound for 20 years. When the patent expires, individuals or companies that can manufacture the same chemical may also pursue FDA approval to market generic versions of the product.

The approval requirements for generic drugs are not as exhaustive as those needed to achieve the original New Animal Drug Approval. A generic manufacturer must accomplish two things. The first is to demonstrate that their version of the compound is chemically identical to the one first approved (known as the pioneer). Proof of chemical identity mostly involves manufacturing issues, which have very stringent regulatory requirements.

The second issue is demonstrating that the generic candidate acts like the pioneer when given to the intended animal species. The preferred method is demonstrating plasma bioequivalence i.e., that both generic and pioneer compounds are metabolized at similar rates and to a similar extent. Plasma bioequivalence was used to test the generic ivermectin pastes that are currently approved for equine use (e.g., Equell, Ivercare, Phoenectin, Rotation 1).

Some drugs, however, are metabolized in a manner that results in negligible or erratic plasma levels. Generic approvals for such drugs can be accomplished by biological end-point bioequivalence testing, which is a modification of the efficacy studies performed initially by the original manufacturer. Bioequivalence is granted if both drugs significantly reduce worm numbers with greater than 90% efficacy. If the calculated efficacy of either compound is less than 90%, bioequivalence can still be granted if the data meet certain statistical criteria. Biological end-point bioequivalence was used to test the generic pyrantel pamoate products currently marketed for horses (e.g., Exodus, Pyrantel Pamoate Paste, PSI's suspension).

If either testing method shows a generic drug to be equivalent to the pioneer, then the generic can receive all the label claims for the same dosage of the pioneer at the time of comparison. Finally, drugs that are solutions (not pastes or suspensions) may require no animal testing, and the generic manufacturer's only burden of proof is chemical identity.

While a patent is in effect, the manufacturer of a drug operates in the absence of competition and can charge what the market will bear. Generic drugs generally can be sold at lower prices, however, because development costs are significantly lower. Although the term "generic" is sometimes used to suggest inferior or inconsistent quality, the chief purveyors of this notion are pioneer manufacturers who hope to maintain their market share. Approval of a generic drug by the Center for Veterinary Medicine of the Food and Drug Administration means, by definition, that it is considered to be equivalent to the pioneer.--*Karen Briggs*

**SAVING A FEW BUCKS: Are Compounded Anthelmintics As Good?**

You might have heard about "compounded" dewormers that are much cheaper than those you can buy from a vet or tack shop. They claim to have the same active ingredient as the national brands, so they should be just as good, right? Often, the answer is no.

Manufacturing veterinary drugs is very complicated; to achieve Food and Drug Administration (FDA) approval, manufacturers must demonstrate that a product consistently matches its label's description. A drug is far more than just the active ingredient. Its safety and efficacy depend on the active ingredient plus all of its other components, which can affect its stability, shelf life, and absorption. Overall product quality depends on the quality of each component.

In many cases, compounded drugs are examples of drug piracy, the act of producing and selling a copy of a drug approved by the Food and Drug Administration (FDA).

Many chemicals used in pirated products are bulk chemicals (usually powders) that come from non-FDA-approved sources. They might be smuggled into the Unites States and have no quality assurances or testing for safety or efficacy. It's nearly impossible for pirates to produce a drug that matches FDA quality, safety, and efficacy standards. According to at least one independent study performed by Merial Limited, pirated ivermectin dewormers have been shown to lack the quality and concentration of the FDA approved products (see "Is Your Horse Getting The Right Medications?," [www.TheHorse.com/ViewArticle.aspx?id=3649](http://www.thehorse.com/ViewArticle.aspx?id=3649)).

The other problem with pirated products is that if the drug fails to work or harms your horse, you as an owner have no recourse because drug piracy and the use of these products is illegal. With dewormers, you might not even know the pirated product hasn't done what you expected it to do; the consequences might not be apparent for several months.

Pharmacists can legally compound veterinary drugs *if* there are no FDA-approved drugs for the problem. Given the various dewormers and formulations (pastes, gels, suspensions, solutions, pelleted top-dress) available, that's clearly not the case, so it's hard to conceive of a situation that would justify using a compounded anthelmintic. The main motivation seems to be price. Remember, you usually get what you pay for. Caveat emptor (buyer beware).

The reappearance of eggs in the manure will generally take about four weeks if you’ve used pyrantel or one of the benzimidazoles, six to eight weeks if you’ve used ivermectin, and 12-16 weeks with moxidectin. These numbers will also depend on the horse—youngsters and those carrying very heavy parasite loads will generally have eggs reappear more quickly.

Back in January, in our first installment of this series, we described what makes a parasite different from other kinds of infectious organisms. One of those factors is that the offspring of adult parasites must return to the environment outside the horse in order to become capable of infecting a second animal, or re-infecting the original host.

So while discussing the environment might seem esoteric when we're talking about equine parasites, it's really one of the most critical elements to consider if you're going to construct an effective anti-parasite strategy. Equine parasites must undergo some change away from the horse--so the environment presents unique opportunities for disrupting transmission. That's a tremendous advantage compared with diseases that are directly contagious from one horse to the next.

The key to exploiting environmental events is understanding when and how Mother Nature works--for us or against us--in our perpetual battle against worms.

**Environmental Factors**

So what qualifies as "environment" for your horses? In the case of most domestic horses, the answer would be stalls, pastures, and paddocks. These are the battlefields on which we wage war against our major parasitic enemies--strongyles (bloodworms), ascarids (roundworms), and tapeworms.

Environment in a broader sense includes literally anything outside of the equine host. So, for certain equine parasites such as stomach worms and *Onchocerca* (which we discussed in the May issue), the flies that transmit them also must be considered a part of the environment.

Let's briefly review the changes undergone by each of the three major parasites during their sojourn in the environment.

Strongyles, ascarids, and tapeworms all produce an egg stage that passes from the horse in manure. Ascarids (as we discussed in the March 2004 issue) lay eggs that can develop to the infective stage in two to four weeks. The potential new roundworm is protected within the egg, and it can remain infective for perhaps as long as a decade. Strongyle eggs (see the April 2004 issue) hatch over a wide range of temperatures, and the rate of development varies with thermal conditions. The first-stage larva that emerges from the egg feeds in the environment, and it eventually molts to a second- (L2) and a third stage (L3) larva. Only the third stage is potentially infective to another horse.

Tapeworm eggs (February 2004 issue) must be eaten by free-living mites found on pasture. They then develop into the infective stage (cysticercoid) inside the mite. All three parasites are transmitted into your horse when he inadvertently ingests the infective stage while grazing in the pasture.

**Microenvironmental Variables**

Temperature, moisture, and the availability of oxygen all have the potential to affect parasite development in the environment. Let’s take a detailed look at each one. *Temperature—*Ascarid and strongyle eggs are capable of developing or hatching over a wide range of environmental temperatures. As a general rule, the rate of development increases in direct proportion to the environmental temperature. Thus, strongyle eggs can hatch at 45°F, but it could take several weeks for them to reach the infective (L3) stage. At 80°F, however, strongyle larvae can become fully infective within five days of eggs leaving the horse. There are two dynamic processes going on here. The first is development, which is the formation of new infective stages from a reproductive product (egg). The environmental conditions that favor parasitic development are virtually identical to those required for germination of a plant seed. Both respond to the same conditions—they will germinate (hatch) and grow above some critical temperature, but the rate of growth is accelerated in warmer conditions. Development is only half of the picture for parasite transmission. The other factor is persistence, or how long infective stages survive in the environment. Persistence has a greater impact on the cumulative numbers of parasites acquired, and thus on the likelihood of associated disease. The environmental conditions that influence persistence are nearly the opposite of those required for development. Let’s return to our gardening analogy. After the successful germination and growth of a tomato plant, the gardener can harvest and enjoy the ripe, red fruits. But what conditions would allow her to preserve that tomato for the longest period of time—or in terms of parasites, what conditions would allow them to persist for the longest time in the environment? If the tomato were stored in a refrigerator, it would remain fresh longer than if it were placed out in the sun. This analogy applies directly to the infective stages of many common parasites because they persist far longer at cold temperatures than in warm ones. This difference shouldn’t be a huge surprise to us because equine parasites probably evolved along with their warm-blooded hosts in temperate, rather than tropical, climates. Accordingly, the environmental stages of most equine parasites are more at home on the steppes of Siberia than in the steamy jungles of India or on the sands of Saudi Arabia. Let’s examine this phenomenon by using strongyles as our model. After a strongyle egg hatches, the first- (L1) and secondstage (L2) larvae feed actively in the environment, ingesting organic material and bacteria from the manure. The third-stage larvae (L3), however, which are infective, are covered by a membrane that protects them from desiccation (drying out). This flexible coat of armor contains one major design flaw. It has no mouth opening, so an L3 can no longer feed. It must survive by using stored energy reserves. You’ll never see a nematode with love handles, because they have no organs of energy storage. Their sole energy reserves are stored within tiny intestinal cells, and those are very limited in quantity. The rate of consumption of those finite energy reserves is directly proportional to environmental temperature, meaning that their energy is used up more rapidly in hot weather. Just as in high school chemistry lab, firing up a Bunsen burner and applying heat often sped up a reaction. So, too, worms burn energy faster at higher temperatures—and they die when their energy reserves are depleted. At colder temperatures, energy consumption by third stage strongyle larvae is nil. That is why they survive for months in a refrigerator, and they can persist happily all through winter in most North American climates. Remember that these larvae are cold-blooded invertebrates. They aren’t killed by freezing, they don’t shiver when they get cold, and they don’t need any mechanisms to burn energy in order to stay warm. They just take the weather as it comes and expend their energy in response to thermal conditions. In comparison, ascarids and tapeworms are less susceptible to environmental conditions. Ascarid eggs still need warmth to develop to an infective stage, but a viable egg can survive for up to a decade. Tapeworm eggs might be killed by freezing, but it is certain that their mite vectors only feed actively during the warmer months of the year. This means mites can only ingest eggs (and acquire new infections) during spring, summer, and autumn in most parts of North America. We don’t know how long mites can survive once infected, but it is reasonable to assume that they make it through winter conditions just fine. *Moisture—*Because larval stages are more dependent on moisture than worm eggs, we’ll use strongyles again to explore this environmental variable. Sufficient moisture is usually present in equine manure to support the hatching of strongyle eggs and promote development to the L3 stage if temperatures are warm enough. But when development is slowed, additional moisture might be required to complete development. Because all grazing animals demonstrate some degree of fecal avoidance behavior larvae have a better chance of becoming successful parasites if they migrate away from manure and onto forage where they will be consumed. Larvae can be disseminated by mechanical disruption of fecal piles, but the most common method is through heavy rainfall (anything in excess of a half-inch). Parasite transmission is hindered by drought, but helped along by frequent precipitation. After they leave the fecal pile, most strongyle larvae set up shop in the thatch layer on pasture. This is the dense mat of vegetative detritus (debris) at the root level of pasture grasses, directly on top of the soil. The relative humidity within the thatch layer is considerably higher than in

other areas of the vegetation, especially during dry weather. Because of the critical requirement for a moist microenvironment, strongyle transmission occurs almost exclusively on pastures. Infection from stalls or dry-lot paddocks is negligible—clean horse stalls are simply too dry to allow strongyle larvae to develop or persist, and even in a filthy, damp stall, strongyles are unlikely to develop because the ammonia that comes with urine accumulation is extremely toxic to strongyle larvae. Clean and dry or wet and stinky, horses rarely acquire new strongyle infections in confined conditions. *Oxygen—*Because parasite offspring only become infective in an aerobic environment, they all require oxygen for development and growth. However, sufficient oxygen is uniformly available in all but a few extreme circumstances. The relatively loose structure of equine manure ensures that air can penetrate to all areas of the fecal pellet, especially as it dries out.

**Larval Survival**

Leaving pastures unoccupied for several months of the year might reduce the risk of infection, but remember the seasonal patterns we discussed in “Development and Persistence of Parasites”. Strongyle larvae can survive for only a few weeks during summer, but for as many as six to nine months during colder weather—and few horse owners can afford to leave a contaminated pasture ungrazed long enough for the worm larvae to die of attrition. However, it might be possible to temporarily turn a grazing pasture into a hay field and recover the forage in a baled format. Or you might want to allow nonequid species to graze the pasture for a while. Equine strongyle larvae are quite host-specific; they cannot infect cattle, sheep, goats, camellids (llamas or alpacas), or humans. Given a herd or flock of “alternative livestock” that consumes about the same amount of pasture as your horses, effective parasite control could be achieved by routinely alternating the use of pastures between horses and other species. This is a complex solution, but one that could work extremely well if the species were rotated at intervals that were appropriate for the local climate, i.e., when pasture contamination becomes dangerous for one bunch of residents, it’s time to move them off into another area and bring in the substitutes. A deposit of horse manure in a pasture can serve as a protective reservoir for parasitic larvae if the manure dries gradually over a period of several weeks. Larvae within fecal masses can be evicted from this protected habitat and exposed to desiccation and ultraviolet light by “dragging” or chain-harrowing pastures to break up the manure. However, dragging should only be performed on unoccupied pastures, and only during hot weather. Horses can be put back on dragged pastures to graze within two to three weeks after dragging during summer conditions, but the risk of infection will not decrease until the following spring if pastures are dragged in autumn or winter.