Summary

Numerous and diverse factors can impact the efficacy of anthelmintic (deworming) products used for parasite control in cattle. Different products from various drug classes vary in regard to the route of administration (oral, topical, injectable), solubility, route of excretion by cattle, stability and activity spectrum. Management factors such as administration rates (based on animal weights), treatment timing, record keeping, pasture status and the techniques used for efficacy evaluations also affect the degree of parasite control provided by anthelmintics. Furthermore, the immune status of host cattle plays a critical role in achieving high efficacy from anthelmintic products. Simply put, use of the right product in a proper manner at strategic times will help ensure optimal benefits are derived from parasite control programs.

Key points

• Economically significant anthelmintic efficacy is sometimes not achieved due to numerous factors arising from diverse sources.

• Deworming products perform differently from one another due to variations in product characteristics such as administration route, solubility, excretion, stability and activity spectrum.

• Management factors such as administration rates, treatment timing and pasture status also affect the degree of parasite control achieved.

• The immune status of host cattle plays a critical role in achieving high efficacy from anthelmintic products.

• Implementation of treatment protocols recommended by Pfizer Animal Health can help ensure optimal benefits are derived from parasite control programs.
Producers deworming their animals typically expect an anthelmintic product to work without fail and, subsequently, presume that parasitic worms have been effectively removed from their cattle. However, multiple factors can impact the efficacy of any anthelmintic, and the actual effectiveness of a product may be considerably less than what was expected. “Efficacy” of an anthelmintic product may be defined as the reduction or elimination of a parasite burden that permits the animal to grow and reproduce at its maximum genetic potential (assuming adequate nutrition and general good health). While ideal, such efficacy can sometimes be difficult to attain because of numerous factors arising from sources relating to product characteristics, management and host immunity.

**Product characteristics**

Specific product features and characteristics, such as route of administration, chemistry, pharmacology, etc., can define or limit the efficacy of anthelmintics. Product distinctions include the following:

- **Oral products** — impacted by feed in the rumen/abomasum
- **Topical products** — impacted by licking, dirt and subfreezing temperatures
- **Fat-soluble products** — impacted by body fat concentration
- **Water-soluble products** — impacted by rapid excretion or mode of action (ineffective against inhibited larval parasites)
- **Rapidly excreted products** — impacted by lack of persistent activity
- **Product stability** — impacted by temperature, oxidation and ultraviolet light
- **Limited efficacy against certain parasites** — e.g., cattle and deer flukes, multihost ticks, *Nematodirus*

Before discussing these factors, the impact of the route of administration on product dosing should be understood. In general, only 15 percent to 20 percent of a topically applied anthelmintic will enter the bloodstream of cattle, and the amount rises to about 50 percent for an orally dosed product. In contrast, 85 percent to 95 percent of a parenterally applied anthelmintic will be absorbed into the bloodstream under ideal conditions. These differences are important for understanding why product doses vary based on the route of administration, such as a 0.2 mg/kg dose rate for an injectable macrocyclic lactone (ML) product vs. a 0.5 mg/kg dose rate for a topical form of the same ML product.

**Oral products**

The amount of feed in the gut of cattle will impact the efficacy of oral anthelmintic products. For instance, one study measured blood levels of ivermectin (an ML product) or benzimidazole (BZ) oral products in cattle treated when just coming off feed compared with animals that had been off feed for 24 hours. The recently fed animals demonstrated a 30 percent reduction in both maximum blood levels and total blood levels over 48 hours. Such reductions in drug availability will likely reduce product efficacy.

**Topical products**

When blood levels of topically applied ML products were measured in calves allowed to self-groom or lick other cattle, blood levels (AUC) increased 36 percent compared with control calves, with 10 times more product in the feces. The increased drug availability was due to absorption via the gastrointestinal tract. Clearly, the dynamics of a drug in the animal was impacted by some of the topical drug entering the body orally.

Topically applied fat-soluble products such as MLs depend on transport across the skin through the hair follicles. If hair follicles are blocked with dirt, follicle transport will be reduced. Temperature can be another impediment to proper administration. If some topical ML products are applied at temperatures below 20°F, their viscosity can restrict transport through the hair follicles. This is particularly true for ML products such as moxidectin and eprinomectin, but ivermectin and DECTOMAX® have 75 percent isopropanol in their carriers to improve low-temperature viscosity.

**Fat-soluble products**

Nonpolar products such as MLs depend upon fat as the storage site in the body of the treated animal. If adequate fat is present in the animal, these products (especially ivermectin, DECTOMAX, eprinomectin and moxidectin) will be distributed from the bloodstream into the body fat, with the fat then serving as a reservoir depot. The drug subsequently moves back into the bloodstream as circulating concentrations are depleted by excretion. This process allows for continued product activity against incoming infective larvae for two to five weeks, depending upon the parasite species and specific drug. However, problems can occur if little body fat is present in an animal other than fat in nervous tissues (i.e., the brain). Cases of neurotoxicity have been observed with moxidectin (the most polar ML) when administered at recommended dose rates to young, sick calves (see moxidectin injectable U.S. label warning). Eprinomectin is an exception in the ML class in that it is not stored in fat (aminoacyl group at Position 4).
**Water-soluble products**

Benzimidazole (BZ) anthelmintic products like VALBAZEN®, fenbendazole and oxfendazole are water-soluble, a characteristic that can impact efficacy because they are excreted over a three- to four-day period after administration while MLs are excreted over a four-week period. For instance, BZs administered at 10 mg/kg are not effective when fourth-stage Ostertagia larvae are in deep inhibition (midwinter in Northern areas, midsummer in Southern and West Coast regions), but they are effective during the other nine months of the year. In contrast, products of the ML class are effective any time of the year. Another contributing factor is the fact that the ML mode of action is on the nervous system of parasites while BZs act on their microtubules. When parasites are metabolically active, products that impact either the nervous system or the microtubules will kill the parasite. However, when worms are not metabolically active (in deep inhibition), microtubule function is not required for short-term survival so BZ products will not impact the parasites, but nervous system function is still needed and, thus, MLs retain efficacy (slow excretion and irreversible binding of MLs also are necessary for efficacy when the parasites are not metabolically active).

**Rapidly excreted products**

Fat-soluble drugs are stored in the fat and are primarily excreted through the bile into the intestine, so they remain in the body for two to 10 weeks after administration. In contrast, water-soluble drugs (e.g., levamisole, pyrantel) are quickly excreted through the kidneys and are in the body only one to two days. Intermediate-soluble drugs such as BZs are excreted through both the bile ducts and kidneys and remain in the body for four to five days after administration.

The amount of time that a drug concentration remains at a lethal-dose level (LD₉₀ to LD₉₅) in the bloodstream defines the time period of parasite mortality. Thus, the “killing time” for levamisole is one day, two days for BZs, and one to five weeks for MLs (depending on product and parasite species; see pharmacokinetic profiles and label claims for persistent activity). Binding affinity is also part of this relationship; levamisole binding is quickly reversible, BZ binding is slowly reversible and ML binding is virtually irreversible.

**Product stability**

All marketed products must go through a series of stability studies conducted at freezing temperature, room temperature and high temperature (i.e., accelerated stability studies). The concentration of the active drug component is measured before the product is sealed and again after the study is completed, to detect any environmentally induced decreases in drug potency. The stability of the drug is a function of the oxidation of the molecule, which may be affected by temperature, ultraviolet light, pH, etc. If the molecule has one or more unprotected double bonds (such as MLs), then oxygen and ultraviolet light are often very damaging, especially under conditions above room temperature. As a result, special precautions such as carriers without superoxide radicals and ultraviolet light blockers in the packaging are absolutely critical to achieve product shelf-lives of up to three years. However, one issue not usually addressed is drug stability after protective packaging is breached, such as when a bottle is opened, half or more of the product is used (exposing drug to air in the bottle), product is stored in the back of a pickup or in a hot barn all summer, or the ultraviolet blocker incorporated into the outer packaging (not the bottle) is discarded.

**Limited efficacy against certain parasites**

**Flukes:** Products approved for use in the United States are only effective against young-adult or mature-adult cattle flukes (greater than eight weeks post-infection in cattle). Unless all of the flukes in a host are adults, efficacy will be diminished by the percentage of the fluke population younger than 8 weeks after infection. Therefore, for maximum efficacy of a single dose, treatment should be administered in September in the Southeast and in December in the Northwest because fluke transmission is interrupted when snails hibernate (or estivate) for two months prior to these times. For control of deer flukes, increased dosing is required (e.g., 15 mg/kg of VALBAZEN).

**Multihost ticks:** MLs are effective against several multihost tick species when the parasites are feeding on blood. However, because reinfection from ticks on other species (mice, rabbits, deer, ground squirrels, etc.) can rapidly reinfect treated cattle, treatment may exert little or no impact on the general tick population.

**Nematodirus:** These parasites (especially immature larvae) are generally refractory to acceptable levels of control by MLs, so BZs are the preferred product class for treatment of Nematodirus. Infective Nematodirus larvae prosper during a cool, wet spring, but if the spring is dry, then they remain in the soil and do not expose themselves to young calves until the end of summer when a nonpathogenic challenge may coincide with light grazing, triggering immune responses in
cattle. However, if no exposure occurs in the spring and substantial autumn rains ensue, then high levels of exposure to weaned calves often occur, causing significant pathology to immune-naïve, 9-month-old calves consuming large quantities of grass.

Management factors

Anthelmintic efficacy can be impacted by management issues such as dose rate, efficacy evaluation techniques, timing of doses, feed availability and health status (other than parasites). Products can only be expected to work as defined on the label if a full dose is given to the animal and the particular product characteristics discussed earlier are taken into consideration. However, the techniques by which a “full dose” is determined and how the expected outcome of that dose is measured are equally important factors.

Dose rate

Ideally, all animals should be weighed prior to dosing so the correct dose can be calculated for each individual animal. Unfortunately, this is often impractical outside of a feedlot setting so compromises are made to calculate dosing. The “next-best” method is to group animals by age and visual appearance (e.g., pre-weaned calves, weaned calves, stockers, feeders, heifers/bulls 1 to 2 years old, heifers/bulls 3 to 5 years old, bulls/cows older than 5 years of age). Representative animals within each group should be weighed to establish the heaviest animal in the group, and the entire group should then be dosed as appropriate for the heaviest animal.

Evaluation

To determine expected treatment outcomes in calves younger than 6 months of age, two good parameters may be employed: 1) fecal egg count reduction (FECR) may be utilized unless animals are infected with larval parasites (inhibited or developing); and/or 2) changes in body weight at treatment compared with weaning weight. After 6 months of age, treatment weight compared with body weight five to six months post-treatment is a good parameter. FECR is less reliable (or completely unreliable) for animals older than 6 months of age because worm numbers may not correlate with fecal egg counts.

Record-keeping

Parameters used to assess parasite control efficacy are greatly enhanced by comparing results with a previous year involving similar treatment times in similar-age animals. Although year-to-year variations may be present depending upon feed availability (especially in grazing animals), such year-to-year comparisons can offer a quick evaluation of treatment program success (especially if the products used have changed) while also providing an “early warning” if drug resistance is becoming a factor in an operation.

Timing of doses

The decision of when to dose cattle requires an analysis of the host animals, endemic parasites and drug efficacy. Consider a scenario involving a cow/calf operation in the southeastern United States where weaned calves are grazed to 650 pounds before shipment to a feedlot. Typically, these animals (excluding bulls) would encounter internal gastrointestinal nematodes (peak infections in March) and liver flukes, with horn flies as the primary ectoparasite. Questions that must be addressed include what product to use, at what dose and why.

Assuming the calves are born in February (fall-born calves create a different scenario), treatment of cows in December with an ML product would be appropriate to remove nematodes and minimize infections prior to calving, when the highest stresses and greatest nutritional requirements occur. Calves should be treated with an ML product in late March or April to provide protection from the heavy challenge they would encounter in February and March when grass consumption begins.

In regard to flukes, a typical wet spring means all grazing animals need to be treated in June with a flukacide to prevent mortalities during the summer, and a second dose should be administered in early September. The fall dose represents the most effective time for a fluke treatment since snails (intermediate hosts) would have been estivating through the summer and nearly all of the flukes in cattle would be adults. The June dose may be omitted if the spring is dry. Fencing-off of water holes combined with a molluscicide treatment to reduce transmission also are recommended practices for fluke control. The importance of fluke control before feedlot entry was illustrated by recent research where fluke-infected calves, although treated for flukes at arrival, still demonstrated 0.2 pound per day reduced average daily gain compared with fluke-free calves. For cow/ calf producers intending to market fluke-free calves, an intensive program of four fluke treatments per year for the entire herd, for a duration of at least four years, should be implemented.

Horn fly control becomes imperative in the summer, but control programs are often complicated by issues of resistance to organophosphates and pyrethroids. A useful goal is to keep fly numbers under 200 flies per
animal (the economic threshold). Rotation of products is useful in helping keep chemical classes effective at economically viable levels, and ML pour-on applications have been shown to offer an excellent third component of the rotation programs.8

As autumn rains begin and new grass grows, cattle need to again be dewormed, especially targeting inhibited Ostertagia larvae that have accumulated over the summer. Inhibited larvae cannot be detected by egg counts (since larvae do not lay eggs) and are a major source of appetite suppression in fall-grazing cattle. MLs are the most reliable product category because they are effective against all stages of inhibition, whereas BZs are not effective when the larvae are in deep inhibition.4 Also, immune responses generated by fall vaccination of the calves may be enhanced when worms are removed because CD8 killer cell repression by Ostertagia is relieved.9

The value of strategic parasite control was clearly demonstrated in a Louisiana study involving stocker cattle grazed in the winter and early spring to prepare them for the feedlot.10 Cattle treated twice with DECTOMAX over 140 to 160 days gained 0.42 pound per day more than calves treated only once. These treatment-timing recommendations obviously cannot be translated directly to other areas of the United States. The timing of the various treatments is basically reversed in the northern-tier states since the winter involves lice and inhibited Ostertagia, and the summer and fall have the highest pasture larval counts (infective challenge). The timing is also different for stockers (weaned calves) and feeders.

**Pastures**

Permanent pastures that are continually grazed typically contain high larval parasite counts. Dry, hot weather and, secondarily, dry, cold weather are the greatest deterrents to pasture larvae. If animals are housed or grazed on wheat pasture or cornstalks, or if pasture rotation programs are in place, different treatment strategies and timings also are possible — such as using short-acting products (BZs or levamisole) when placing cattle on clean pastures. Since no larval challenge exists on a clean pasture, the long-acting feature of ML products is not an advantage.

Of course, adequate available grass or another nutrition source are critical prerequisites for maximum productivity of cattle whether parasitized or not. However, treatment benefits are often enhanced in stressed animals, such as drought situations where the nutritional status is poor.

### Host immunity

Cattle can be ranked into a hierarchy of immune competence based on age and parasite challenge. In general, 80 percent of the parasites are found in 10 percent of the cattle in any age group. Cattle can be ranked in the following broad groups.

**Calves (1 to 9 months of age)** — Becoming competent. As calves begin to eat more grass, larvae of several genera of internal parasitic roundworms will be ingested, as will flukes in some areas (ectoparasite immunity will not be discussed here). Under normal stress/nutrition conditions, the immune system will mount an effective immune response over the next three to four months of exposure. However, three classes of immunity should be recognized: innately immune; responder; and nonresponder. “Innately immune” calves respond quickly, never harboring high worm burdens or generating high egg counts. About 10 percent to 20 percent of a normal herd will typically be innately immune. ‘Responder’ cattle become infected, demonstrating high worm numbers and egg counts for about three to four months, but egg counts then decline sharply and worm counts decline slowly over the next three months (with the one exception of Ostertagia). About 60 percent to 80 percent of a normal herd will typically be responders. The remaining 10 percent to 20 percent of the herd are “nonresponders.” These animals achieve high worm burdens and high egg counts that then decline for one to two years. Absolute immunity is never quite reached, especially with Ostertagia, which secretes a substance that down-regulates CD8 killer cells and prevents cattle from eliminating worms from their gastrointestinal tract.

**Cattle (1 to 3 years of age)** — Competent. However, bulls are less competent than cows (testosterone effect), and pregnant cows (especially those close to and after parturition) are less competent than nonpregnant cows.

**Cows (>3 years of age)** — Most competent. Exceptions include cows in late pregnancy through eight weeks after calving.

Product efficacy is a combination of the treatment plus the immune response of the animal. Stressors such as viral infections, shipping, dust, reduced feed availability, etc., may negatively impact the immune system and, thus, the overall treatment efficacy. If stress factors in the production system are negatively impacting the immune system, worm numbers may be abnormally high. A 90 percent reduction in worm
numbers may still leave a large number of worms capable of restricting growth or reproduction of the animals. This would constitute another example where fecal egg counts do not provide the full picture of what is going on within the animal since they are poorly correlated with internal parasite loads.

**Recommended treatment protocols**

More often than not, instances of lessened anthelmintic efficacy (as well as parasiticides in general) are impacted by factors other than resistance or drug activity failure, and some of these factors have been discussed above. Simply put, proper use of anthelmintics, at the proper time of the season, is critical in ensuring effective parasite control.

**DECTOMAX Important Safety Information:** DECTOMAX Injectable has a 35-day pre-slaughter withdrawal period. DECTOMAX Pour-On has a 45-day pre-slaughter withdrawal period. Do not use in dairy cows 20 months of age or older. DECTOMAX has been developed specifically for cattle and swine. Use in dogs may result in fatalities.

**VALBAZEN Important Safety Information:** Cattle must not be slaughtered within 27 days after the last treatment with VALBAZEN. Not for use in lactating dairy cattle. Do not administer to female cattle during the first 45 days of pregnancy or for 45 days after removal of bulls.

5. Rew, personal communication of unpublished data.