

Feed additives: a nutritionist's perspective on their purpose and application

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Abstract

Numerous feed additives are utilized in feedlot diets for various purposes including growth, efficiency, carcass merit, and for prevention and treatment of disease. This article is to review the most common feed additives utilized in feedlot cattle in North America as well as their indications and restrictions. The Veterinary Feed Directive will require veterinarians to understand these principles for feed-grade antibiotics for purposes of writing prescriptions in coordination with colleague nutritionists.

Key words: cattle, feedlot, feed additives

Résumé

De nombreux additifs alimentaires sont utilisés dans les diètes de parcs d'engraissement pour diverses raisons, dont la croissance, l'efficacité, la carcasse du mérite, et pour la prévention et le traitement de la maladie. Cet article est d'examiner les plus communs d'additifs alimentaires utilisés dans un parc d'engraissement des bovins en Amérique du Nord ainsi que leurs indications et restrictions. La directive vétérinaire pour les aliments exigera des vétérinaires de comprendre ces principes pour antibiotiques fourrager pour fins de rédaction de prescriptions en coordination avec collègue nutritionnistes.

Feed Additive Definitions

Medicated feed additives are categorized by FDA.⁶ Category-I drugs are those that require no withdrawal period at the lowest use level in each of the species for which they are approved. Category-II drugs require a withdrawal period at the lowest use level for at least 1 species they are approved for or are regulated at a "no-residue" or "zero-tolerance" basis. FDA also defines 3 types of medicated products. A Type-A medicated article is a product of standardized potency which is destined for production of a Type-B or Type-C medicated feed. A Type-A medicated feed is typically the feed article that comes directly from the drug manufacturer and is the most concentrated form of a product that can be used by feedlots. If a Type-A drug is used at a feedyard, it would be fed from a microingredient machine which batches with high accuracy and precision. In order to use a Type-A, Category-II drug, a feed manufacturing facility must have an approved and active Medicated Feedmill License (MFML); these include

feed additives such as amprolium, tilmicosin, and zilpaterol. A Type-B feed is also intended for the production of other Type-B and -C feeds, but it also has a substantial quantity of other nutrients such as vitamins and minerals which dilute the Type-A article. A Type-C medicated feed is produced by substantial dilution of the Type-A or -B medicated articles and may be offered as a complete feed to the animals. We would typically consider the diet that we manufacture at the feedlot and deliver directly to a pen of cattle the Type-C feed.

The maximum concentration of active ingredient allowed into the Type-B of Category-I and -II drugs is 200 and 100 times the continuous use level, respectively.⁶ For example, the maximum level of ractopamine, a Category-I drug, in a Type-C feed is 24.6 g/ton (90% DM basis). Consequently, the maximum level allowed in the Type-B is 2.46 g/lb. Similarly, the maximum level of zilpaterol, a Category-II drug, in a Type-C feed is 6.8 g/ton (90% DM basis); consequently, the maximum level allowed in the Type-B is 680 g/ton or 0.34 g/lb. It is also important to note that use levels can be defined in terms of concentration (e.g. mg/kg or g/ton) and/or dosage (mg/day or mg/lb of body weight per day). In many cases, a drug will have use levels in terms of both concentration and dosage. This can become challenging to meet both dosage and concentration requirements on some drugs, such as tylosin and tilmicosin. It is also important to know that most label requirement concentrations are expressed on a 90% DM basis; however, most diets are formulated on a 100% DM basis. Consequently, care must be taken to ensure that units are on the same basis. For example, ractopamine can be fed up to 24.6 g/ton (90% DM basis) in cattle; this is equivalent to 27.3 g/ton on a 100% DM basis. Moreover, feed tags for mixed feeds, supplements (e.g. Type-B) are expressed on an as-is basis.

It is also important to note the language on the feed additive labels. For example, some labels state to feed the product "continuously as the sole ration". This means that the feed additive is to be fed in every feeding the animals get during the described labeled period. Also note that drugs can only be fed in combinations with other drugs if it listed as an approved product.⁶ This also means that if 2 drugs are not approved to be together in the same diet, they cannot be in the same feed bunk together on the same day even if they were batched separately. For example, monensin and chlortetracycline cannot be in the same feed bunk together on the same day.

In the last few years FDA has released 3 guidance documents pertaining to the use of feed-grade antibiotics. FDA Guidance 152 categorized antibiotics into categories

on the basis of their use to treat enteric food-borne pathogens and their importance in treating human disease. These categories are 1) critically important, 2) highly important, and 3) important. Of the common feed additives used in the US cattle, macrolides (tylosin and tilmicosin) were listed as critically important. Tetracyclines (chlortetracycline and oxytetracycline) and streptogramins (virginiamycin) were listed as highly important; these are also feed additives. Feed additives not listed as medically important include ionophores, anti-coccidials, bambermycin, and bacitracin. FDA Guidance 209 defined judicious use of antibiotics and included steps to limit their use to only those uses needed to assure animal health, and not for purposes of growth and efficiency. FDA Guidance 213 lays out the plans and timeline for establishment of VFDs for medically important antibiotics such as tylosin, chlortetracycline, oxytetracycline, virginiamycin, and tilmicosin (tilmicosin is already under VFD).

Ionophores, Anti-Coccidials, and Other Non-Medically Important Feed Antibiotics

Ionophores

Ionophores are non-medically important antibiotics which are not used in human medicine and are commonly used in traditional grazing and feedyard nutritional programs. The name ionophore is derived from “-phore”, meaning to carry or bear, and “ion”, meaning a positively- or negatively-charged atom. Therefore, ionophores facilitate the carrying and exchange of ions across cellular membranes in human and bacterial cells. As a result, this exchange alters the osmotic balance of cells. The rumen in cattle is comprised of millions of bacteria which are responsible for the fermentation of feed, specifically carbohydrates from grain and forage, into byproducts including short chain fatty acids, commonly referred to as volatile fatty acids (VFA), as well as methane, carbon dioxide, and heat. The primary VFAs produced in the rumen are acetate, propionate, and butyrate, and they are then utilized by the body to convert to energy primarily in the form of glucose and long-chain fatty acids. Of the VFAs, propionate is the most efficient in terms of retaining more energy in the rumen (i.e. less lost as carbon dioxide and methane) as well as due to its entry point in the tricarboxylic acid cycle, which results in less loss as carbon dioxide. Consequently, propionate is the preferred VFA to be produced. Ionophores favor the production of propionate by shifting the bacterial population in the rumen. Gram-negative and gram-positive bacteria exist in the rumen. Gram-positive bacteria have a simple membrane structure whereas gram-negative bacteria have a complex outer membrane. This complex outer membrane in gram-negative bacteria prevents ionophores from acting in the inner membrane; however, ionophores can act on the simple outer membrane of gram-positive bacteria. Although there are slightly different modes of action of various ionophores, they primarily work by attaching to the membrane of gram-positive bacteria and creating a channel to move sodium and hydrogen ions into the cell. In an effort to

maintain osmotic equilibrium, the cells pump potassium and hydrogen out.³ As a result, the pH in the cell drops and osmotic pressure increases, which causes a futile cycling of ions across the membrane, depletion of ATP, and cellular rupture, all of which result in cellular death and decreased proliferation of some gram-positive bacteria as well as protozoa, the latter of which are involved in coccidiosis. Consequently, gram-negative bacteria become a larger proportion of the bacterial population in the rumen. This shift in population results in bacteria which produce more propionate, resulting in improved efficiency of feed utilization and improved cattle performance. Due to their mode of action in affecting cellular ion exchange and osmosis, care must be used to prevent mixing mistakes which can cause damage to cardiac muscle, especially in horses.

In the US, 3 ionophores are approved; monensin (Rumensin[®]), lasalocid (Bovatec[®]), and laidlomycin (Cattlyst[®]). For up-to-date information, please review current FDA label indications and combination clearances.⁶ Monensin-Type A is currently formulated to have 90.7 g/lb (i.e. 20%). For cattle fed in confinement, monensin has an indication for improved feed efficiency to be fed at a concentration of 5 to 40 g/ton (90% DM basis) and at a dosage of 50 to 480 mg/animal daily. Monensin also has an approval for prevention and control of coccidiosis at a concentration of 10 to 40 g/ton (90% DM basis) to provide 0.14 to 0.42 mg/lb of bodyweight (BW) up to a dosage of 480 mg/animal daily. Monensin has cross-clearances with other feed additives such as tylosin, melengestrol acetate, decoquinate, ractopamine, zilpaterol, and tilmicosin in cattle (refer to FDA clearances for more information).

Lasalocid-Type A is manufactured in various concentrations. Although lasalocid has primarily been used for cattle in grazing situations, lasalocid has an indication for improved feed efficiency for cattle fed in confinement and is to be fed at a concentration of 10 to 30 g/ton (90% DM basis) and at a dosage of 100 to 360 mg/animal daily. Lasalocid is also approved for control of coccidiosis for cattle up to 800 lb at a concentration of 30 to 181.8 g/ton (90% DM basis) to provide 1 mg/2.2 lb of bodyweight (BW) up to a dosage of 360 mg/animal daily. Lasalocid has cross-clearances with other feed additives such as chlortetracycline, oxytetracycline, melengestrol acetate, and tylosin in cattle (refer to FDA clearances for more information).

Laidlomycin-Type A is currently formulated to have 50 g/lb (i.e. 11%). Laidlomycin is indicated for improved feed efficiency to be fed at a concentration of 5 to 10 g/ton (90% DM basis) and at a dosage of 30 to 150 mg/animal daily. Unlike the other 2 approved ionophores, laidlomycin does not have an approval for control of coccidiosis. Laidlomycin has a cross-clearance with chlortetracycline in cattle (refer to FDA clearances for more information).

Non-Medically Important Feed Antibiotics Used for Growth

Although not an ionophore, bambermycin (trade name GAINPRO[®]; flavophospholipol) is not used in human medicine and is classified as non-medically important. Bambermycin

is a glycolipid antibiotic that inhibits peptidoglycan synthesis and cell walls in bacteria.² Bambermycin-Type A is currently formulated to have 10 g/lb (i.e. 2.2%). For cattle fed in confinement, bambermycin is indicated for improved feed efficiency and rate of weight gain and is to be fed at a concentration of 1 to 4 g/ton (90% DM basis) and at a dosage of 10 to 20 mg/animal daily. Although approved for prevention of coccidiosis in chickens, bambermycin is not approved for such use in cattle. Bambermycin has no cross-clearances with other feed additives in cattle (refer to FDA clearances for more information).

Non-Ionophore Anti-Coccidials

Parasitic protozoa such as *Eimeria bovis* and *Eimeria zuernii* can cause morbidity and mortality in cattle. These protozoa are called coccidian and can be ingested via consumption of infected water, feed, or fecal material or via direct contact with infected animals, so it is a very contagious disease. Once ingested, sporozoites are released from sporocysts by digestive enzymes in the small intestine and then asexually reproduce creating merozoites which then undergo cell division and then sexual reproduction in the large intestine to form oocysts.⁷ These oocysts and resulting ruptured intestinal cells are then passed in the feces, and the oocysts can be sporulated which can then start a vicious cycle of infecting cattle. Amprolium (trade name Corid[®] and Amprol[®] 25%), is an anti-coccidial compound that is a thiamine analog. It blocks the thiamine receptor in coccidia, which then blocks thiamine uptake and its role as a cofactor in carbohydrate metabolism needed for the rapid division and reproduction of coccidia. Amprolium-Type A is currently formulated to have 113.4 g/lb (i.e. 25%). Amprolium is indicated for prevention and treatment of coccidiosis, and is to be fed at a concentration of 113.5 to 11,340 g/ton (90% DM basis) and at a dosage of 5 mg/kg of BW daily for 21 days for prevention or 10 mg/kg of BW daily for 5 days for treatment. Additionally, a 24-hour withdrawal is required when using this product. Amprolium has no cross-clearances with other feed additives in cattle (refer to FDA clearances for more information).

Decoquinatate (trade name Deccox[®]) is also an anti-coccidial compound that is a quinolone derivative. Decoquinatate inhibits sporozoite development by inhibiting DNA gyrase and, hence DNA synthesis.⁷ Decoquinatate-Type A is currently formulated to have 27.2 g/lb (i.e. 6%). Decoquinatate is indicated for prevention of coccidiosis, and is to be fed at a concentration of 12.9 to 535.7 g/ton (90% DM basis) and at a dosage of 22.7 mg/100 lb of BW daily for at least 28 days. Decoquinatate has cross-clearances with chlortetracycline, monensin, and tylosin in cattle (refer to FDA clearances for more information).

Liver Abscess Antibiotics

Tylosin (trade name Tylan[®] and Tylovet[®]) is a macrolide antibiotic which binds to the 50S ribosomal subunit of

bacteria and inhibits linking of amino acids and elongation in protein synthesis.⁵ For similar reasons as ionophores, tylosin has greater effectiveness against the less complex membrane structure of gram-positive bacteria. Macrolides are considered **critically important** in FDA Guidance 152 due to their importance in human medicine, and tylosin is commonly fed to cattle. Tylosin-Type A is currently formulated to have 40 or 100 g/lb (i.e. 8.8 or 22.0%). Tylosin is also indicated for reduction of liver abscess incidence caused by *Fusobacterium necrophorum* and *Truuperella pyogenes* (previously known as *Arcanobacterium* or *Actinomyces pyogenes*), and is to be fed at a concentration of 8 to 10 g/ton (90% DM basis) and at a dosage of 60 to 90 mg/animal daily. Tylosin has cross-clearances with other feed additives such as monensin, lasalocid, melengestrol acetate, decoquinatate, ractopamine, and zilpaterol in cattle (refer to FDA clearances for more information).

Virginiamycin (trade name V-Max[®]) is a streptogramin antibiotic which consists of mixtures of 2 separate structurally distinct compounds, type A and B. Similar to tylosin, streptogramin-A binds to the 50S ribosomal subunit of bacteria preventing elongation of protein. This binding allows for greater binding affinity of streptogramin-B, which then can cause more amino acids to be released during elongation of the protein.⁵ Streptogramins are considered **highly important** in FDA Guidance 152 due to their importance in human medicine; however, virginiamycin is not commonly fed to cattle. Virginiamycin-Type A is currently formulated to have 50 or 227 g/lb (i.e. 11 or 50%). Virginiamycin is indicated for reduction of liver abscesses and is to be fed at a concentration of 13.5 to 16 g/ton (90% DM basis) and at a dosage of 85 to 240 mg/animal daily. Virginiamycin has no cross-clearances with other feed additives in cattle (refer to FDA clearances for more information).

Bacitracin methylene disalicylate (trade name BMD[®] and Pennitracin MD[®]) is a polypeptide antibiotic which mainly affects gram-positive bacteria by decreasing the synthesis of bacterial walls and also increasing the permeability of bacterial cell walls, which leads to cell death.⁸ Bacitracins are **not** considered medically important in FDA Guidance 152, and are not commonly fed to cattle. Bacitracin methylene disalicylate-Type A is currently formulated to have 30, 50, 60, or 75 g/lb (ie 6.6, 11.0, 13.2, or 16.2%). Bacitracin methylene disalicylate has an indication for reduction in number of liver condemnations due to abscesses and is to be fed at a dosage of 70 mg/animal daily throughout the feeding period or at 250 mg/animal daily for 5 consecutive days followed by discontinued use for the next 25 days and then repeating this cycle throughout the feeding period. Bacitracin methylene disalicylate has no cross-clearances with other feed additives in cattle (refer to FDA clearances for more information).

Tetracyclines such as oxytetracycline (trade name Terramycin[®] and Pennox[®]) and chlortetracycline (trade name Aureomycin[®] and Pennchlor[®]) are in their own class and primarily act to inhibit protein synthesis in bacterial cells by binding to receptors on their 30S ribosomal subunit, result-

ing in prevention of protein chain elongation.⁴ Tetracyclines are considered **highly important** in FDA Guidance 152 due to their importance in human medicine, and tetracyclines are commonly fed to cattle. Tetracyclines, both oxy- and chlortetracyclines, are manufactured at numerous concentrations in Type-A formulations. In addition to other indications described in the subsequent section, tetracyclines do have an indication for reduction of liver condemnation due to liver abscesses and is to be fed at 70 mg/animal daily for chlortetracycline or 75 mg/animal daily for oxytetracycline. Chlortetracycline has some cross-clearances with other feed additives such as sulfamethazine, decoquinat, laidlomycin, and lasalocid in cattle (refer to FDA clearances for more information). Oxytetracycline has a cross-clearance with lasalocid in cattle (refer to FDA clearances for more information).

Bovine Respiratory Disease Feed Antibiotics

Tetracyclines (oxytetracycline and chlortetracycline) and a macrolide (tilmicosin) are also approved for respiratory ailments in cattle. Chlortetracycline has indications for control of bacterial pneumonia associated with bovine respiratory disease (BRD) at a target dosage of 350 mg/animal daily. Chlortetracycline is also indicated for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* organisms at a target dosage of 10.0 mg/lb BW daily for not more than 5 consecutive days. Similar to chlortetracycline, oxytetracycline has indications for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* organisms at a target dosage of 10.0 mg/lb of body weight daily for 7 to 14 consecutive days.

Tilmicosin is indicated for control of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in situations where active BRD has been diagnosed in at least 10% of the animals in a group. Additionally, tilmicosin cannot be used concurrently or subsequent to administration of an injectable macrolide or within 3 days of administration of a non-macrolide; it can only be fed within the first 45 days of the production period. When utilized under these criteria, tilmicosin must be fed at a dosage 12.5 mg/kg of BW daily with a dietary concentration of 568 to 757 g/ton (100% DM basis) for a 14-day period and as the sole ration. A 28-day withdrawal must also be adhered to following this use of feed grade tilmicosin. Tilmicosin Type A is currently formulated to have a concentration of 90.7 g/lb (ie 20%).

Estrus Suppression

Melengestrol acetate is a steroidal progestin fed to suppress the expression of estrus in heifers. Melengestrol acetate has a structure that is very similar to progesterone, blocking ovulation and estrus while follicular growth and estrogen production are not inhibited. Melengestrol acetate moder-

ates the release of luteinizing hormone from the pituitary gland which maintains the follicular development without formation of corpus luteum. Consequently, endogenous estrogen levels are maintained, and growth rate is enhanced.² Melengestrol acetate Type A is marketed under the trade names of MGA[®] and HeifermaX[®]. MGA is currently formulated to have a concentration of 200 and 500 mg/lb while HeifermaX is formulated to have concentration of 500 mg/lb. Melengestrol acetate is indicated for increased weight gain, improved feed efficiency, and suppression of estrus (heat) and is to be fed at a dosage of 0.25 to 0.50 mg/animal daily. Melengestrol acetate has cross-clearances with other feed additives such as monensin, tylosin, lasalocid, decoquinat, ractopamine, and zilpaterol in cattle (refer to FDA clearances for more information).

Beta-Adrenergic Agonists

Beta-adrenergic agonists have been approved for use in beef cattle in the US for almost a decade. Beta-adrenergic agonists are analogs of the catecholamine hormones epinephrine and norepinephrine. The 2 beta-agonist hormones that are currently FDA-approved in North America for use in finishing beef cattle are ractopamine hydrochloride (Optaflexx, Elanco Animal Health, Greenfield, IN; Actogain, Zoetis, Kalamazoo, MI) and zilpaterol hydrochloride (Zilmax; Merck Animal Health; Summit, NJ). Ractopamine was approved by FDA in 2003 and marketing began in 2004. Zilpaterol was approved in 2006 and then received combination approval with monensin and tylosin in 2008. Actogain, a generic ractopamine, was approved in 2013. Both beta-agonists are to be fed continuously until harvest; however, ractopamine must be fed as the sole ration unless utilizing the top-dress clearance. Ractopamine is to be fed the final 28 to 42 days of the feeding period and does not have a withdrawal period. Additionally, ractopamine can be fed either on a dosage or concentration basis up to 27.3 g/ton (100% dry matter basis) in combination with monensin and tylosin. Depending on intake this equates to a maximum of approximately 300 mg/animal daily. Ractopamine can also be fed in a top-dress form up to a maximum of 400 mg/animal daily. Zilpaterol can be fed for the final 20 to 40 days of the feeding period immediately prior to harvest, and then must be withdrawn for at least 3 days to ensure tissues meet the FDA residue clearance requirements. Currently, zilpaterol can be fed on a concentration basis at 7.56 g/ton (100% dry matter basis) or on a dosage basis targeting between 60 and 90 mg/animal daily; the latter is a component feeding claim. These beta-agonists can be incorporated into finishing diets either in the concentrated Type-A form (Optaflexx & Actogain = 45.4 g ractopamine/lb; Zilmax = 21.77 g zilpaterol/lb) or in a diluted Type-B supplement which is typically manufactured by a third-party mill. The manufacturer that uses the Type-A zilpaterol product to prepare a Type-B zilpaterol supplement or a Type-C zilpaterol complete feed must be a licensed feed

mill. In contrast, a feedmill license is not required to feed a Type-B supplement containing ractopamine or zilpaterol or to feed Type-A ractopamine. Feedyards with a licensed feedmill license that use Type-A ingredients have microingredient machines to add these ingredients to the diet.

Conclusions

It is important to understand the purpose, indications, and restrictions for use of feed additives. Review the feed additive labels, the Feed Additive Compendium, and your nutritionist colleague when making recommendations to ensure these feed additives are being utilized properly.

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