Practical and applied use of veterinary feed directives in production

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Abstract

Feed additives are important tools for livestock producers to improve animal health, wellbeing, and productivity in modern livestock production. Feed additives used for the improvement of efficiency, weight gain, and carcass characteristics have been well documented in the literature. Feed additives with animal health implications require a more diligent approach to use, and therefore require a higher level of evaluation. There are numerous labels, combinations, and dose ranges associated with feed additive use. In the current regulatory environment, the understanding of these labels and how to effectively implement the compounds which require veterinary feed directives in a practical manner is important to both those who create the directives, and those who implement them. Practical, cost-effective decisions with respect to the use of in-feed antimicrobials are multi-faceted and complex.

Key words: feed additives, veterinary feed directive, medicated feed

Résumé

Les additifs alimentaires sont des outils importants pour les producteurs de bétail afin d'améliorer la santé, le bien-être et la productivité dans les élevages modernes de production. Les additifs alimentaires utilisés pour améliorer l'efficacité, le gain de poids et les caractéristiques de la carcasse ont bien été documentées dans la littérature. L'utilisation d'additifs alimentaires ayant des implications pour la santé animale requière une approche plus assidue et donc une évaluation à un plus haut niveau. Il existe plusieurs étiquettes, plusieurs combinaisons possibles et un éventail de doses associés à l'utilisation d'additifs alimentaires. Dans le contexte actuel de réglementation, connaître ces étiquettes et savoir comment mettre en œuvre de façon pratique les composés qui nécessitent des directives pour aliments vétérinaires sont importants à la fois pour ceux qui émettent les directives et pour ceux qui les mettent en œuvre. Prendre des décisions pratiques et plus économiques concernant l'utilisation d'antimicrobiens dans l'alimentation comporte plusieurs facettes et est complexe.

Introduction

Medicated feed additives (**MFA**) were first introduced for livestock disease control and production enhancement in the mid-1940s.[12] As agricultural systems and livestock production technology advanced, many new compounds were investigated and commercialized. New classes of compounds that could be included in feed were discovered, some of which not only had animal health application, but also produced improvements in productivity and weight gain. At present, many compounds exist as tools for livestock producers to improve health, production, and thus, economic efficiency within operations.

Generally, MFA fall into 2 categories: 1) products utilized for disease treatment and prevention; and 2) products utilized to improve feed efficiency, weight gain, and carcass characteristics. Some of these products, such as ionophores, are useful for coccidiosis prevention as well as improving productivity through modification of the rumen microflora. Other production-enhancing MFA work through directing nutrients to lean tissue deposition, or via modification of natural hormonal cycles to suppress estrus. These technologies have proven to be cost-effective, valuable tools in modern livestock production.[27]

Regarding the use of in-feed antimicrobials, growing governmental concern and consumer interest about antimicrobial resistance of importance to human medicine led to more diligent oversight to ensure judicious use of these compounds in food animal production. Thus, in 2017, veterinary feed directives (**VFD**) became mandatory for all medically important antimicrobials **(MIAs)** to be included in feeds administered for livestock production.

Categories of Medicated Feeds

While the use of in-feed MIAs requires a VFD, there are several other non-MIA MFAs available commercially with a myriad of combination clearances. Many of these combination clearances exist in conjunction with in-feed MIAs that require VFDs. Therefore, it is incumbent upon the veterinarian to have a firm comprehension of what regulations exist with respect to MFA that require VFDs as well as what combinations are allowed in conjunction with the product of interest.

The US Food and Drug Administration[9] organizes labeling with respect to MFA into 2 categories. They can be classified as either Category I, which require no withdrawal period or Category II, which are drugs that require a withdrawal period at the lowest use level for at least 1 species that they are approved for. Most commonly used MFA in cattle production fall under Category I, and a bulk of what will be

discussed in the current manuscript will be in reference to Category I MFA. The FDA also categorizes feeds containing MFA into 3 categories. Type A medicated articles are those used to manufacture other Type A medicated articles and/or used to manufacture Type B/C medicated feeds. Type B medicated feeds are used in the manufacturing of other Type B or Type C medicated feeds. Type C feeds are usually intended to be fed as a complete feed or used to manufacture other Type C feeds as a top dress or free-choice supplement.

The designation of differing types of feed categories is important due to varied dose ranges approved across each of the indications for use. These are most commonly differentiated between Type B and Type C feeds. It should be noted that co-clearances can differ for MFA used in either Type B or Type C feeds, where a co-clearance exists for Type C but not Type B feeds. Those writing VFDs should understand and be familiar with the definitions used by FDA-CVM.

Veterinary Feed Directives and Application

There are several medically important MFA commonly utilized in dairy and beef production including macrolides, tetracyclines, and some streptogramins. The following discussion relative to practical considerations when utilizing these compounds will primarily focus on application of macrolides and tetracyclines in medicated feeds. As mentioned in the previous text, based on the type of medicated feed utilized in an operation the grams/ton concentration and/or (if applicable) the mg/hd/d indication for the use of several of these medicated feeds may differ slightly and therefore require a different concentration on the VFD. Secondarily, one must be cognizant that indications for various concentrations of some VFD products may be on a 100% dry matter (**DM**) basis or a 90% DM basis. Additionally, some labels may not address DM percentage for dosing products altogether. In practical terms, it is important to understand what implications this may serve in terms of the magnitude and frequency with which VFDs may need to be updated, corrected, or changed within commercial operations.

Several in-feed antimicrobials are approved for reduction in liver abscess rates in cattle fed in confinement for slaughter. These are bacitracin methylene disalicylate, chlortetracycline, oxytetracycline, tylosin, and virginiamycin. The most common in-feed product used in cattle fed in confinement for slaughter is tylosin phosphate (**TYL**).[20] Tylosin phosphate is approved to be fed continuously for the reduction in liver abscesses in steers and heifers fed in confinement for slaughter. Several studies evaluating the use of TYL have demonstrated a reduction in liver abscess rates[3] compared with a negative control. Tylosin has demonstrated a decrease in incidence of liver abscess rates ranging from 40 to 70%.[15] Of compounds currently commercially available, TYL is the most effective at reducing liver abscess incidence, with other MFA demonstrating a reduction less than TYL.[15] The mode of action for reduction of liver abscess via TYL occurs primarily through the inhibition of *Fusobacterium necrophorum* in the rumen. Because of its categorization (macrolide) as an antimicrobial of critical importance with respect to human health use (FDA), TYL is only allowed under the issue of a VFD. Although a VFD is required for its use in confined feeding situations, TYL is still widely used among feedlot operations. The approved dose ranges for TYL make it difficult in some situations to effectively maintain an accurate dose of the compound and remain within approved ranges. For example, TYL is approved to be fed at a rate of 8 to 10 g/ton (90% DM basis) to provide 60-90 mg/hd/d (no DM referenced on label). This may present challenges in terms of accurately staying within labeled doses in situations of very high (i.e., >24 lb [11 kg] DMI) or very low intake (i.e., <12 lb [5.4 kg] DMI) periods on an operation. For cattle with relatively low DM intake, in order to provide the minimum approved dose on mg/hd/d basis (60 mg/hd/d), one might have to increase the concentration of the product and thereby exceed the 10 g/ton maximum allowed dosage in the feed. Conversely, in cattle with very high intakes, the minimum concentration approved in feed (8 g/ton; 90% DM basis) may result in animals consuming greater than 90 mg/hd/d. Due to the restrictive nature of the label dose of TYL it is imperative that veterinarians issuing VFDs coordinate with the nutritionist/feed company formulating the rations as well as FDA inspectors to clarify if both dose ranges cannot be met, which is the most important criteria? In some cases, direction has been issued to meet the mg/hd dose range rather than the g/ton concentration in the feed (personal communication). From a practical standpoint, meeting the mg/hd dose criteria makes sense from a judicious use standpoint, rather than a concentration in the feed.

The tetracycline class of MFAs has been widely used as a therapeutic in-feed treatment for several bacterial-related diseases in cattle production. Tetracyclines are categorized as highly important antimicrobials from a human health perspective and therefore require a VFD for use in feed. Chlortetracycline (**CTC**) and oxytetracycline (**OTC**) are the most common of this class utilized in beef and dairy operations. Other products have approval as combinations of CTC and OTC with other antimicrobials (CTC + sulfamethazine; neomycin + OTC). Chlortetracycline has approvals for control of bacterial pneumonia associated with shipping fever complex (350 mg/hd/d), treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* (10 mg/lb [22 mg/kg] BW up to 5 days), and control of active infection of anaplasmosis caused by *Anaplasma marginale* (350 mg/hd/d for <700 lb [318 kg] stocker/pasture animals; 0.5 mg/lb [1.1 mg/kg] BW for >700 lb [318 kg] stocker/pasture animals). Oxytetracycline has similar, albeit slightly different, approvals in cattle. These include treatment of bacterial enteritis caused by *E. coli* and pneumonia caused by *P. multocida* susceptible to OTC (10 mg/lb [22 mg/kg] BW for 7 to 14 days).

While these have a broad range of approvals and may provide some ease of use in feed, it is important to weigh the

cost effectiveness of the use of these products compared with other potentially more effective parenteral antimicrobials. This can present a complex decision-making process that should include determinations of the baseline mortality, historical or expected mortality of the population in question, morbidity (expected or current), logistical constraints at the operation, reduction of stress to the animal by additional handling, husbandry practices that may alleviate the need for antimicrobials in the operation, current inventory cost of the animals to be treated, and current antimicrobial protocols. Likewise, for cow-calf producers who may investigate the use of CTC for control of anaplasmosis, how likely is the disease to affect the herd in question, has it been detected in the region, and what will the cost be to provide this product across every animal in question?

Relative to the use of tetracyclines in confined settings, Szasz et al evaluated the use of either CTC administration at 4 g/hd/d for 3 5-d therapeutic regimes compared with 14 consecutive days of OTC administration at 4 g/hd/d beginning at 10 DOF in calf-fed Holstein steers (arrival weight 310 lb [140.9 kg]). These in-feed antimicrobial regimes were conducted in conjunction with tulathromycin (TUL) metaphylaxis on arrival compared to TUL alone or CTC feeding alone. Szasz et al observed decreased morbidity in populations receiving CTC and TUL compared with those receiving OTC and TUL, CTC alone, or TUL alone.[24] No differences were observed between treatments for overall mortality or BRD-related death loss. It should be noted that overall mortality for cattle used in the study was 1.98%. Additionally, there was no negative control treatment to determine what the baseline mortality might have been had no antimicrobials been given. Therefore, although there was a benefit in terms of reductions in morbidity with CTC administration, the baseline mortality rate in this population may have been too low to accurately determine the effectiveness of CTC administration on overall mortality. Similarly, cattle only administered CTC (those that did not receive TUL at arrival) had a mortality rate that was 1.92%, which was numerically lower than the average across the study. Duff et al observed similar effects when evaluating the use of CTC in combination with either arrival or pre-shipping administration of tilmicosin phosphate (**TIL**).[7] When TIL was administered on arrival in conjunction with a therapeutic dose of in-feed CTC in beef calves, the authors observed lower morbidity compared with those animals not receiving CTC. These same researchers reported no death loss in the study, thereby suggesting that the risk classification of the cattle may not have been high enough to warrant CTC therapy and/or determine what a true contribution of CTC use would be on mortality. Additionally, pen size in the study was relatively small (10 to 11 hd/pen), which in some cases may impact rate of disease transmission when compared with larger commercial operations with greater pen sizes.

While some benefits to the use of CTC in production systems on morbidity have been reported, there may also be indirect performance benefits to the animals. Booker et al reported improvements in performance with the administration of metaphylactic TUL on arrival in beef cattle.[2] This would suggest that when antimicrobials are determined to be the appropriate course of action for a particular population, creating a healthier overall population may also help improve performance later in the feeding period through reductions in morbidity and mortality. Some authors have reported increased intake and ADG from the use of CTC, or CTC and sulfamethazine in combination on newly received beef cattle.[10,13] This observation is most likely due to improving the overall health of the population through reduced morbidity and mortality, thereby creating a population that likely consumed more feed throughout the feeding period.[5]

Given the variable outcomes associated with mortality and the use of MFA, it is important to identify the cost effectiveness of these products in combination with or without the use of metaphylactic microbials used on arrival. For example, with a cost of $0.06/g of CTC and an animal inventory cost of $800.00 for a 500 lb (227 kg) steer, absolute mortality would need to be decreased by approximately 0.188% to break even with the cost of one 5-day therapeutic treatment with CTC at 10 mg/lb (22 mg/kg) BW ($1.50/hd total cost). If 2 5-day therapies are needed ($3.00/hd total cost for both regimes), the absolute mortality reduction necessary to break even would be 0.376%. This simple example only looks at impacts on mortality, and does not take into account ancillary benefits, such as decreased morbidity or secondary improved performance, which may or may not exist depending on the baseline risk factors for the population of interest.

In-feed MIAs are also commonly used in milk replacers at dairy calf rearing facilities.[11] Approvals for commonly used in-feed MIAs include OTC for the treatment of bacterial enteritis caused by *E. coli* susceptible to OTC; CTC for the treatment of bacterial enteritis caused by *E. coli* susceptible to CTC; neomycin/OTC for the treatment of bacterial enteritis caused by *E. coli* and for control of colibacillosis caused by *E. coli* susceptible to neomycin. Care must be taken when determining what products fall under these specific approvals, as many combination products exist in the market that may not qualify under these approvals. While the combination of neomycin and OTC is approved for use in milk replacers, some neomycin products are only approved for the treatment of calves on an *individual* basis rather than through batching of an MIA in milk replacer for populations or groups of calves to be fed. Additionally, some labels may allow for batches of treatments in a water-soluble form to treat animals individually via water drench or in a divided watering application. In this scenario, the product would be used under a water-soluble approved method, thereby requiring a veterinary prescription rather than falling under the requirement of a VFD.

The use of OTC/neomycin combination product has been reported to reduce morbidity and mortality in calves challenged with *E. coli* during the initial 7 days in the rearing facility.[18] The authors noted improved health parameters and attitude score, suggesting that MFA in milk replacers can be

beneficial under these conditions. The authors did note that the animals received no other antimicrobial treatment on arrival, and therefore the cost effectiveness in combination with other injectable antimicrobials is not known. Similar to examples in confined feeding and/or stocker operations, one must carefully consider the potential animal health risk classification, inventory cost, and other antimicrobial metaphylactic interventions that may provide ancillary benefits as compared to the use of MFA for therapeutic purposes.

Tilmicosin phosphate is available as an in-feed product for use in cattle confined for slaughter. The VFD requirements associated with in-feed TIL use are relatively restrictive as compared to some more broad-spectrum in-feed MIAs. In-feed TIL is approved for the control of bovine respiratory disease associated with *Mannheimia haemolytica, P. multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group. Additionally, in-feed TIL cannot be used under a VFD if the population intended for treatment has been administered a macrolide or within a 3-day period of a non-macrolide. This approval requires that if TIL in feed is to be used it must occur within 45 d of arrival to the facility, and the course of TIL treatment is for a single 14 d period. Effectively, the restrictions on the in-feed use of TIL make it very difficult to 1) find populations of cattle that would fit these criteria and 2) if populations are identified, determine that in-feed TIL is more cost-effective than parenteral use of other licensed antimicrobials to control BRD. If a population of cattle arrives at a facility with a risk profile large enough to warrant 14 d in-feed antimicrobial therapy, then it stands to reason that the population may benefit greater from the use of an injectable metaphylactic macrolide at arrival. If the population is deemed low-enough risk that metaphylaxis is not required, but then has morbidity exceeding 10%, an intervention with an injectable macrolide at the individual animal level utilizing some sort of diagnostic test (such as rectal temperature) for BRD may be a more judicious use than in-feed treatment.

Feed Additives in Production

Ionophores

Ionophores are some of the most commonly used MFA in cattle production to date[20,25] for disease control and preventative for coccidiosis and for improvements in weight gain and feed efficiency. The most common ionophores in use with feed efficiency and weight gain approvals are monensin sodium (**MS**), lasalocid sodium (**LS**), and laidlomycin propionate (**LP**). The improvements in feed efficiency and weight gain are attributable to selection for gram-negative bacteria and subsequently greater propionate production in the rumen.[1] The animal absorbs this propionate and converts that VFA into glucose, thereby improving energy retention and feed efficiency. The shift in the microbial population is also responsible for a decrease in ammonia production and more efficient microbial crude protein production in the rumen. Improvements in microbial efficiency allow for greater microbial crude protein to pass on to the hindgut for absorption. Due to increased microbial protein flow to the small intestine ionophores such as MS for example, elicit a "protein sparing" effect in the rumen.[1] The improvements in feed efficiency attributable to MS, LS, and LP administration range between 3 and 6% in confined settings when cattle are fed high-concentrate diets.[8,22,26] Some of the improvement in feed efficiency may be explained by reductions in subacute, ruminal acidosis, due to inhibition of major lactic acid-producing bacteria like *S. bovis*[16] and reduced intake variation.[23] The effects of ionophores on ruminal fermentation, reducing ruminal fluid viscosity, and reducing intake variation are also positive for controlling bloat mortality in both feedlot and grazing cattle.[4]

Additionally, both MS and LS are approved to be fed to cattle in pasture settings for increased weight gain. Monensin has also shown improved milk production efficiency in dairy cattle.[14] Both MS and LS are approved for prevention and control of coccidiosis with differing minimum effective doses of 0.14 mg/lb (0.31 mg/kg) of BW and 0.455 mg/lb (1.0 mg/kg) BW, respectively.

Coccidiostats and Antimicrobial Rumen Modifiers

Other MFA that are approved for prevention and control of coccidiosis (*Eimeria bovis* and *Eimeria zuernii*) are decoquinate and amprolium. While amprolium is approved for a prevention dose (2.27 mg/lb [5 mg/kg] BW), it is the only MFA commercially available with approval for treatment of clinical coccidiosis (4.54 mg/lb [10 mg/kg] BW) at a higher dose in cattle.

Bambermycin is another MFA characterized as a rumen modifier that has demonstrated some production efficiency.[21] These improvements primarily occur through increases in gain and/or efficiency compared with a negative control.

Performance Enhancing MFA

Melengestrol acetate (**MGA**) has been used as an MFA in heifers fed in confinement for slaughter since the 1950s. The primary mode of action for MGA is through suppression of estrus in intact heifers. The prevention of estrus serves to decrease the net energy of maintenance of the animal and results in improved slaughter weight, carcass weight, weight gain, dry matter intake, reduced riding behavior, improved average daily gain, feed efficiency, and greater quality grade compared with no administration of MGA, as well as lower BRD related mortality in heifers fed MGA compared to heifers not fed MGA.

Beta-agonists, such as ractopamine, act as repartitioning agents that direct nutrients away from fat deposition and toward lean tissue deposition. This generally occurs through an increase in protein synthesis and/or a decrease in protein degradation. There are 2 beta-agonists currently approved for use in the US, zilpaterol hydrochloride (**ZIL**) and racto-

pamine hydrochloride (**RAC**). Zilpaterol, while approved, has been voluntarily pulled from the market and is no longer commonly used in the US. Ractopamine hydrochloride is commonly utilized in beef cattle production and is labeled to be fed the final 28 to 42 days-on-feed in steers or heifers fed in confinement for slaughter. Ractopamine hydrochloride is labeled for improvements in weight gain and feed efficiency, as well as improvements in carcass leanness.

Conclusion

There are many MFA licensed for use in cattle production and these technologies improve the profitability and sustainability of operations throughout North America by improving animal health and increasing production. However, products requiring VFDs should only be used in a manner that presents the most cost-effective and judicious application and in the best interest of not only operation but also the animal's well-being.

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