March 13, 2017

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: FDA-2016-D-2635, The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, Establishing Appropriate Durations of Therapeutic Administration, Request for Comments

The National Cattlemen's Beef Association (NCBA), the oldest and largest national trade association for cattlemen and women in the United States, in collaboration with the bovine veterinary medical groups, the Academy of Veterinary Consultants (AVC), and the American Association of Bovine Practitioners (AABP) as well as with the National Milk Producers Federation (NMPF), representing dairy producers and their cooperatives which produce the majority of the milk supply for the United States (U. S.), all appreciate the opportunity to provide comments to the request by the Food and Drug Administration (FDA) for information concerning the establishment of appropriately targeted durations of use for the medically important antimicrobial drugs administered in the feed or water of food-producing animals for therapeutic purposes. Through voluntary Guidance for Industry (GFI) #213, FDA defines the uses that are associated with the treatment, control, and prevention of specific diseases to be therapeutic uses that are necessary for assuring the health of food-producing animals.

FDA, in the notice for information published in the *Federal Register* on September 14, 2016, requests specific duration of use information for the following diseases in cattle: **anaplasmosis**, **bacterial enteritis**, **liver abscesses**, and **pneumonia** and for the following antimicrobial drugs: **chlortetracycline**, **oxytetracycline**, **tylosin**, **neomycin with oxytetracycline** and **virginiamycin**. We understand that FDA's questions concerning the practices for establishing duration of use for the above-listed medically important antimicrobial drugs used in food-producing animals are being advanced as part of the agency's efforts to protect public health and promote judicious antimicrobial drug uses. In seeking improvements with antimicrobial stewardship, FDA has broad authority to ensure the safety and use of antimicrobial drugs in animal agriculture. At the same time, FDA does not have the authority to regulate animal husbandry, farming activities, or the practice of veterinary medicine. Antimicrobial stewardship and the responsible use of antimicrobial drugs is dependent upon the cooperation and collaboration of multiple stakeholders. Flexibility in labeling allows veterinarians, who hold the primary oversight responsibility for antimicrobial drug use, to make appropriate risk-based

treatment decisions that address the multiple variables often present for disease risk. Producers are very willing to work closely with their veterinarians to follow prescribed veterinary treatment protocols that result in disease control and eradication[1].

As stakeholders, we understand and appreciate that the development of antimicrobial duration of use recommendations, when there is no duration of use on the existing label, represents an evolving science. Modern animal agriculture is highly innovative and has a proven record of benefiting from the adoption of new technologies. Currently, there are many promising antimicrobial alternatives under investigation and we await the approval for use of many of these alternative agents in cattle. At the same time, the arbitrary assignment of antimicrobial use durations, without reasonable alternatives or demonstrated effective durations for use, presents a threat to animal health that is not acceptable.

We all recognize the need for responsible antimicrobial drug use in food-producing animals to protect public health and to ensure that animal health technologies remain viable for the future. Beef producers have incorporated antimicrobial stewardship guidelines into our industry-driven Beef Quality Assurance (BQA) program. Currently, the BQA program includes a separate manual, ***Antibiotic Stewardship for Beef Producers***[2], designed to provide an easily referenced source of best practices for antimicrobial drug use in the cattle industry. Antibiotic stewardship has been a commonsense practice adopted by beef producers since before the start of the BQA program; the first ***Beef Producers Guide for the Judicious Use of Antimicrobials in Cattle*** was adopted well over 25 years ago.

Likewise, dairy producers have incorporated antimicrobial stewardship guidelines in the industry-driven National Dairy FARM Program: Farmers Assuring Responsible Management. For nearly 30 years, the U.S. dairy industry has focused educational efforts on the judicious use of antimicrobial drugs through the annual publication of the National Dairy FARM ***Milk and Dairy Beef Drug Residue Prevention Reference Manual***[3]. The National Dairy FARM ***Animal Care Manual*** details guidelines and best practices for all dairy cattle care issues and includes requirements for a Veterinarian-Client-Patient-Relationship and a Herd Health Plan, both of which are important for the U.S. dairy industry's antimicrobial stewardship program[4].

For cattle producers, beef quality depends upon raising healthy cattle and calves and producing a safe and wholesome food product. In the National Beef Quality Audit (2011), ninety-six percent of producer respondents believed that they could influence beef quality through activities such as preventive health care practices for cattle[5]. Antimicrobial drugs are only one tool used by producers and their veterinarians to prevent, control, and treat animal diseases. For drug labels with no defined duration of use, the duration of use of medically important antimicrobial agents used in food-producing animals is most often established through the advice of a veterinarian after completing an evaluation of the factors for disease risk. In the National Beef Quality Audit (2011), ninety percent of responding producers reported having a working relationship with a veterinarian.

As outlined in FDA's GFI #213, the agency believes that it is important to include veterinary oversight in the use of the medically-important antimicrobial drugs in the feed or water of food-producing animals. Veterinarians play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to prevent, control, and treat disease. FDA states in GFI #213, "The judicious use of medically important antimicrobial drugs in feed or water of food-producing animals needs the scientific and clinical training of a licensed veterinarian."[6]. We would contend that the need for veterinary oversight for antimicrobial use expressed by FDA also applies to the need for veterinary expertise and clinical judgment to be freely applied to the questions of duration of use for antimicrobial drugs in feed or water through available flexibility in labeling for the defined duration of use. A drug label cannot always adequately define the particular time of disease risk for all disease situations and assess the involved variables in order to consistently achieve optimal patient outcomes. Furthermore, in the case of antimicrobial use in the feed of food-producing animals, extra-label drug use is not permitted and prescriptive drug labeling for duration of use, without clear guidance on the optimal duration, could serve to adversely constrain veterinary clinical judgments. The critical variables in determining a specific duration of therapy are best evaluated by the prescribing veterinarian working individually with the producer to achieve successful disease management.

One Health recognizes that the health of people is connected to the health of animals and the environment. Successful public health interventions require the cooperation of human, animal, and environmental health communities. Healthy animals result in wholesome and safe food for consumers. Maintaining optimal animal health involves the prevention, control, and treatment of animal diseases. The September 2014 President's Council of Advisors on Science and Technology (PCAST) Report to the President on Combating Antibiotic Resistance comments on the importance of disease prevention: "Disease prevention is a laudable goal. Prevention of infection in animals can improve food safety for humans...."[7] Additionally, FDA's Center for Veterinary Medicine (CVM) has stated that preventive antimicrobial use is appropriate when: (1) there is evidence that the drug will be effective in treating the particular disease, (2) such preventive use is consistent with accepted veterinary practice, (3) the use is intended to address particular bacteria, (4) the use is appropriately targeted to animals at risk of developing a specific disease, and (5) there are no reasonable alternatives for intervention.[8] Several of the drug indications and antimicrobial drugs requested for review in the FDA's notice for information meet these criteria for appropriate use and are frequently involved in the prevention or control of animal diseases. In investigating targeted uses, it should be noted that limiting the availability of medical interventions to prevent and control animal diseases on the farm will directly impact global food security and safety as well as animal and human health.[9] As the drug indications for which the agency has requested information each represent unique disease management challenges, we have provided the information in a disease-by-disease response below, followed by a synopsis of the research evidence for specific durations of antimicrobial use.

Anaplasmosis

Bovine anaplasmosis, caused by the rickettsial organism *Anaplasma marginale*, infects the erythrocytes (red blood cells) of cattle and other ruminants[10]. Infected erythrocytes are destroyed by the host immune system resulting in anemia. Severity of clinical signs increases with the age of the animal; in cattle less than 2 years of age, clinical disease is generally mild. In older animals, clinical signs are generally more severe and may include icterus, fever, abortion, weight loss, and mortality rates of up to 49% in naïve adult cattle. While surviving animals become immune to reinfection, they remain persistent carriers for life and serve as an important reservoir for infecting other animals[11].

Bovine anaplasmosis is primarily transmitted through biological vectors (ticks)[12] and distribution of the disease is strongly associated with the geographical and seasonal presence of ticks. The disease is endemic in tropical and subtropical areas worldwide[13]. In the United States, bovine anaplasmosis is enzootic throughout the southern Atlantic and Gulf Coast states, as well as several Midwestern and Western states. Cases of bovine anaplasmosis have been reported in almost every state of the continental U.S.[14]. However, biological vectors are not the only means of transmitting anaplasmosis, as mechanical transmission through other biting insects[15] and blood-contaminated instruments (needles, tattooing instruments, ear tagging devices) used for routine animal husbandry practices has been demonstrated[16,17].

Currently in the United States, oral chlortetracycline products are approved without a defined duration of use for "control of active infection of anaplasmosis". There are no oral tetracycline products approved in the United States for elimination of the anaplasmosis carrier state[18] and use of injectable products to clear persistent carriers has not consistently proven to be effective[19]. While some published experimental studies have claimed to successfully clear the anaplasmosis carrier state through in-feed administration of chlortetracycline, many of the regimens used are not approved in the United States and are therefore prohibited by U.S. law[20]. Outside the United States, imidocarb and gloxazone are used for the treatment of anaplasmosis in cattle. However, neither product is approved by the U.S. Food and Drug Administration for use in cattle and there are clinical concerns with the use of both compounds; Imidocarb (Imochem-120[1]) requires a lengthy slaughter withdrawal period of 90 days in cattle[21], while toxicity to the animal host is high with gloxazone[22].

Typically, duration of therapy with in-feed chlortetracycline for control of bovine anaplasmosis would be prescribed based on the period of risk for infection. This assigned duration would primarily reflect the length of the vector season for a herd in a given geographical area, i.e. in some areas the vector season may be a few months, while in other areas ticks are found throughout the year, therefore, therapy for control may consist of year-round chemoprophylaxis. Additionally, the "vector season" for a particular geographic area is not a static situation. There are reports that tick vector ranges are expanding into new geographical

[1] Imochem-120, interchemie, The Netherlands

areas, presumably due to climatic change[23]. These climate-vector trends were recently supported in an analysis of anaplasmosis diagnostic submissions in Kansas, where minimum land surface temperature, diurnal temperature range (difference between daily minimum and maximum temperatures) and relative humidity were found to be significantly associated with increasing cases of bovine anaplasmosis[24]. Veterinarians and cattlemen would also consider the possibility of naïve cattle moving into the herd and the risk of mechanical transmission outside the vector season when selecting an appropriate duration of chlortetracycline for control of bovine anaplasmosis.

There are few effective alternatives to antimicrobial therapy for the control of anaplasmosis in the U.S. cattle industry. Other than tetracycline antimicrobials, control strategies utilized worldwide with varying degrees of success include intensive arthropod vector control, immunization against both the rickettsial pathogen and the arthropod vector and maintenance of *Anaplasma marginale*-free herds[25].

There are a number of disadvantages to using intensive tick control by means of acaricide (pesticide) application. To maintain adequate control of the arthropod vectors, frequent pesticide application (up to 52 times per year) is used in areas such as South Africa where the disease is enzootic[26]. Beyond the obvious environmental impact of frequent pesticide use, this practice reduces the overall level of immunity resulting in a herd that is more susceptible to disease introduction or reintroduction. If tick control measures fail, either due to disruption of acaricide application or the development of acaricide resistance[27] or if mechanical transmission occurs via other insect vectors or surgical, tagging, or tattooing instruments, a clinical outbreak of anaplasmosis is likely.

Vaccination, against both the infectious organism, *Anaplasma marginale,* as well as the tick vectors, has been used to a limited extent to control this disease worldwide. In the United States, there was an avirulent, live vaccine conditionally licensed by the USDA[28], however, this vaccine is no longer available. A killed experimental vaccine is currently available by special approval, however early versions of the vaccine were contaminated by bovine cells and reportedly induced serious adverse events (neonatal isohemolytic anemia) in calves that ingested colostrum from immunized cows. The ability of vaccines to provide cross protection against different strains of *Anaplasma marginale* has also been shown to be of limited benefit[29]. A recombinant vaccine that induced host immunity to the tick gut antigen Bm86 was developed in the 1990s. Although not currently available in the U.S., field experiences in Cuba, Australia and Mexico with this vaccine have shown promise in decreasing tick burdens and reducing the use of acaricides[30].

As a sole control measure, maintaining an anaplasmosis-free herd status has not proven to be an effective management strategy for this disease, primarily due to poor sensitivity of most diagnostic tests for animals in the early stages of infection[31]. Without sufficiently sensitive diagnostic tools, new additions to a herd cannot be adequately screened prior to introduction into

the group. Biosecurity measures alone also fail to provide complete protection as the insect vectors easily cross fences and boundaries between infected and non-infected herds.

Anaplasmosis is a threat to U.S. cattle production with no effective, USDA or FDA-approved alternatives to antibiotics for control of this disease. While *A. marginale* can infect cattle of all ages and production classes, the need for antimicrobials to control clinical anaplasmosis in a specific group is highly dependent on a variety of risk factors. A label-defined duration of use that does not allow veterinarians flexibility to consider these factors will, invariably, result in antimicrobial exposures that are longer than necessary in some herds, while shorter than necessary in others.

Bacterial enteritis

Enteritis, commonly referred to as "scours", is one of the leading causes of mortality in pre-weaned beef and dairy cattle in the United States[32]. While enteritis can be caused by an array of parasitic, viral and bacterial pathogens, *Escherichia coli* is a significant cause of diarrhea in young cattle. When *Escherichia coli* is the primary cause of enteritis, calves are generally between 1 day and two weeks of age[33], but cases have been documented in calves as old as 4 months of age[34]. Additionally, studies have demonstrated that regardless of animal age and etiology, *Escherichia coli* bacterial numbers are greatly increased in the small intestines of calves with naturally occurring diarrhea[35]. Increased numbers of coliform bacteria in calves with diarrhea has been associated with altered small intestinal function, morphologic damage and increased risk of bacteremia[36].

Clinically, young calves afflicted with *E. coli* enteritis will have profuse, watery diarrhea. In the early stages of the disease, calves rapidly become dehydrated, resulting in weakness, hypothermia, tachycardia or bradycardia, and if left untreated, death from shock and heart failure[37]. In most situations, bacterial enteritis is sporadic within a herd and individual animals are treated with supportive measures consisting of maintaining hydration and an adequate plane of nutrition until the condition resolves. However, antimicrobial therapy of groups of calves may be indicated when conditions such as inclement weather or poor colostral intake result in overwhelming pathogen load in the environment or low levels of overall immunity within a group, respectively. Typically, duration of therapy in these cases would be short (days to a few weeks) and therapy would be discontinued when initiating factors subside.

In cattle production, the primary alternative to antimicrobial therapy of bacterial enteritis in calves has been, and will continue to be, prevention programs focused on vaccination of late gestation cows to enhance colostral immunity, ensuring the adequacy and quality of colostrum intake and decreasing the load of enteric pathogens in the environment through hygiene and pen/pasture management[38,39,40]. While immunization of dams with *E. coli* bacterins has been shown to protect calves from experimental colibacillosis disease challenge[41], handling of pregnant cows is logistically difficult[42], as is ensuring ingestion of colostrum by newborn calves. Management practices to reduce the environmental pathogen load have been widely adopted by

the cattle industry, however, pasture conditions / hygiene are often dictated by unpredictable weather patterns.

Currently, a bovine coronavirus-*Escherichia coli* antibody product[2] is approved as an aid in the reduction of morbidity and mortality from scours caused by K99+ *E. coli*. The primary limitation of this alternative is that, to be effective, it must be administered to the calf within the first 12 hours after birth; a requirement that limits the product's utility in pasture-based operations where calves are often born unattended.

Bacteriophages have been investigated as an alternative therapy for bacterial enteritis in calves and other veterinary species[43,44]. In experimental studies, phage treatment within 8 hours of bacterial challenge reduced mortality associated with neonatal diarrhea; phage treatment at the onset of clinical signs did not provide the same level of protection. Although timing has an impact on the clinical efficacy of bacteriophage therapy, the primary limitation of phages as an alternative to antimicrobials is their specificity for particular bacterial subtypes. In these studies, bacterial isolates were recovered post-therapy that were "resistant" (bacterium-phage mismatched) to the administered phages. Other disadvantages to bacteriophages are that they: require a favorable phage-target bacterium ratio [multiplicity of infection], must be administered parenterally to be effective, and could potentially transduce unwanted genes to zoonotic pathogens[45].

Competitive enhancement strategies, such as probiotics and prebiotics use the activities of the native microbial ecosystem against pathogens. Probiotics are live microorganisms that must adhere to and colonize the gastrointestinal tract, resulting in antagonism against pathogenic bacteria. A prebiotic is a non-digestible food ingredient that selectively stimulates the growth of native probiotic bacteria[46]. Investigations regarding the use of these technologies in cattle has primarily been to increase production efficiency and reduce the transmission of food-borne pathogens, specifically *Escherichia coli* O157:H7, rather than treatment or prevention of animal enteric disease[47]. Data to support the widespread use of probiotics as therapeutics in both human and veterinary medicine have not been definitive, and currently, these compounds are not market-ready for enteric disease therapy indications[48,49]. In studies where probiotics reduced the incidence of diarrhea, the product was administered daily to young calves; this poses a significant logistical challenge that would likely impede the adoption of this alternative for pasture-based beef operations. The use of prebiotics in cattle has seen even more limited uptake due to the density and diversity of the rumen microbial population compared to monogastric animals, the expense of these products and the ability of the ruminant digestive tract to degrade currently utilized prebiotic compounds[45].

Antimicrobial therapy is a valuable tool to manage bacterial enteritis when uncontrollable factors, such as weather or calf immunity, result in outbreaks of the disease. In these situations, the epidemiologic progression of disease through the group will vary considerably depending on

[2] First Defense®, Immucell Corp., Portland, ME

resolution of the inciting factors and how quickly infection control practices can be implemented. Any label-specified duration of therapy should allow for flexibility to consider these factors.

Liver Abscesses

The precise mechanism by which liver abscesses occur is complex and not completely understood. Several studies have demonstrated a strong association between the incidence of rumen lesions and liver abscesses[50,51]. It is generally accepted that rapid fermentation of grains results in ruminal acidosis which, in turn, leads to rumenitis and disruption of the protective surface of the rumen. This disruption allows bacteria to penetrate the rumen wall and access the portal circulation, whereby they are filtered by the liver leading to abscess formation[52]. Given that grain diets are a risk factor for the development of ruminal acidosis, the incidence of this disease is highest in feedlot cattle; however, dairy cattle and other ruminants are also at risk for development of liver abscesses[53]. Liver abscesses pose significant animal welfare and economic concerns to the beef industry in the United States, as approximately 20% of livers are condemned at slaughter primarily due to liver abscesses[54].

Bacterial cultures of bovine liver abscesses generally yield polymicrobial growth with a predominance of anaerobes. *Fusobacterium necrophorum*, an opportunistic pathogen that normally inhabits the ruminant gastrointestinal tract, is considered the primary bacterial agent. *Trueperella* (*Arcanobacterium*) *pyogenes* is often isolated along with *Fusobacterium necrophorum* from liver abscesses, as well as a variety of other anaerobic and facultative bacteria[55].

Currently, chlortetracycline, neomycin with oxytetracycline, oxytetracycline, tylosin and virginiamycin are approved without a defined duration of use in the United States for "reduction of incidence of liver abscesses" or "reduction of liver condemnation due to liver abscesses". The use of feed grade antimicrobials in the production setting has been shown to significantly reduce the incidence of liver abscesses in cattle[56,57,58,59]. As liver abscess development is associated with consumption of high grain diets and ruminal acidosis, these antimicrobials are generally administered continuously to cattle throughout the confined feeding stages of beef production.

As antimicrobial stewardship practices within the beef industry have continued to evolve, the use of these antimicrobials throughout the entire feeding period has come into question. In 2004, an application was filed with the U.S. Patent office by JL Montgomery that protected a particular feeding program to increase beef production and reduce the incidence of liver abscesses, while reducing the total use of macrolide antibiotics (tylosin)[60]. The patented feeding method uses a combination of an ionophore (an antibiotic class not used in human medicine) and a macrolide until the final 20-40 days of the feeding period, at which time the antibiotic combination was removed and replaced with zilpaterol (a ß-agonist). Data presented in the patent application demonstrate a statistically significant reduction in the prevalence of liver abscesses at slaughter with this feeding program. The beef industry is also anticipating the

results of several industry-funded field studies that are near completion, evaluating the potential for alternatives to antimicrobials and current dosing regimens that may prove efficacious in controlling liver abscesses in cattle.

Prevention of liver abscesses has traditionally been based on the use of: 1) antimicrobial feed additives, 2) vaccination, and 3) nutritional management as alternatives to antimicrobials[53]. Vaccination against *Fusobacterium necrophorum* to reduce the incidence and severity of liver abscesses in cattle has been intensively studied, with published study results generally equivocal. In one study, vaccination with a crude leukotoxin vaccine was associated with a reduced incidence, but not severity, of experimentally- induced liver abscesses[61]. In two separate studies, an *Arcanobacterium* (now *Trueperella*) *pyogenes / Fusobacterium necrophorum* bacterin-toxoid reduced the incidence and prevalence of liver abscesses. The reduction in liver abscesses was comparable to tylosin-treated calves when the natural challenge was mild; however, tylosin was statistically better at reducing liver abscess prevalence under severe challenge[62]. In yet another study comparing two commercially available products: 1) a *Fusobacterium necrophorum* bacterin and 2) a bacterin-toxoid containing inactivated *Fusobacterium necrophorum* leukotoxin / *Arcanobacterium* (now *Trueperella*) *pyogenes* pyolysin, both failed to reduce either the incidence or severity of liver abscesses in a production setting[63].

Because of the strong association between liver abscesses and ruminal acidosis, various nutritional management strategies, such as, gradual adaptation to high-grain diets, feeding multiple times per day, providing adequate bunk space and increasing the roughage content of the diet, have been adopted by the feedlot industry[64]. While nutritional management as a disease prevention strategy cannot be understated, there is a lack of consensus as to the specific recommendations, i.e. type of roughage, amount of roughage in the diet and timing (in regard to the feeding period) of roughage feeding that will optimally reduce the incidence of liver abscesses[65]. To date, nutritional management strategies have not been developed that can match the effectiveness of antimicrobials in reducing liver abscesses.

Our understanding of the pathogenesis of liver abscesses in cattle is still incomplete, which has hampered efforts to completely define periods of risk for disease and limited the ability to design effective alternative interventions. As research efforts continue to close these knowledge gaps, refined durations of therapy can be evaluated. Assigning durations of use for control of liver abscesses outside of a science-based approach poses an unnecessary risk to both animal and human health.

Pneumonia

Pneumonia, also known as bovine respiratory disease (BRD), is one of the leading causes of morbidity and mortality in cattle, affecting approximately 16% of feedlot calves and 12% of unweaned dairy heifers in the United States[66,67]. While the underlying pathophysiology of this disease is complex, pneumonia develops following periods of stress induced by multiple

factors such as; transport, comingling (mixing cattle from different sources), dietary changes, rapid weather changes and exposure to respiratory pathogens. These factors predispose cattle to infection by any number of bacteria, however, *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* are considered the primary bacterial organisms responsible for pneumonia[68]. Clinical signs of pneumonia in cattle range from mild lethargy, inappetance, increased nasal discharge and slightly increased respiratory effort to severe respiratory distress and acute death[69]. Early signs of disease are mild and non-specific, making proper diagnosis of pneumonia in cattle a serious challenge to treatment and control efforts[70,71]. When an outbreak of BRD occurs, initial cases generally appear at 7-10 days after calves arrive in a feedlot, with peak disease incidence at day 20. For dairy animals, development of BRD is less predictable, but risk is also associated with periods of stress, such as weaning and transport. These disease timelines can be altered significantly by previous immunization, movement through multiple procurement settings or continued introduction of animals into the group[72].

Chlortetracycline is approved for use in feed for "control of bacterial pneumonia associated with shipping fever" without a defined duration of therapy. A Canadian study demonstrated that inclusion of a chlortetracycline / sulfamethazine combination product in the ration for the first 56 days of feeding significantly reduced bovine respiratory morbidity rate, first relapse rate and chronic pneumonia rate[73]. In a recent study, in-feed administration of chlortetracycline for 5 days significantly reduced animal morbidity, while also reducing the use of antibiotics deemed critically important to human health without increasing the occurrence of antibiotic-resistant *E. coli*[74]. A 5 day regimen of chlortetracycline would be the most common duration for control of bacterial pneumonia, owing to the fact that some chlortetracycline products[3] currently carry this label duration.

Improved biosecurity and enhanced immunity of the individual animal have been proposed as means to replace antimicrobials or reduce the amount of antimicrobials used for treatment and control of pneumonia in cattle production. Vaccines are used widely in the beef and dairy industry to protect against the viral pathogens that often initiate pneumonia in cattle and a recent meta-analysis confirmed that use of these vaccines does decrease the risk of BRD morbidity in natural exposure trials[75]. According to the most recent National Animal Health Monitoring System (NAHMS) survey for beef, 96% and 92% of cattle were vaccinated against respiratory diseases *at arrival* in large (>1,000 head) and small feedlots, respectively[76,77]. However, generation of a protective immune response following vaccination is not immediate and a recent review highlights that the timing of and conditions in which vaccines are administered is critical to their effectiveness[78]. While the NAHMS survey reported that some or all of the cattle were vaccinated *prior to* arrival in a high percentage (>85%) of large feedlots, less than 30% of survey respondents perceived pre-arrival vaccination as "extremely effective" at

[3] NADA 141-250. Aureomycin® and Bovatec®. Zoetis, Inc.

reducing morbidity and mortality in the feedlot. Likewise, the majority of dairy operations vaccinate heifers to immunize against the viral pathogens of bovine pneumonia[79].

The evidence for efficacy of *bacterial* vaccines (bacterins) to reduce the risk of morbidity associated with bovine pneumonia is not as convincing, with many studies demonstrating little to no effect on BRD[80,81,82]. These conclusions were supported by a meta-analysis evaluating the effectiveness of BRD bacterins in feedlot cattle where the data trended toward "no effect" when these vaccines were administered on arrival[83].

Recently, a DNA-liposome immunostimulant[4] was introduced as an antibiotic alternative to aid in the treatment of bovine pneumonia when administered at the time of a perceived stress event. This product was shown to statistically reduce lung lesions and mortality from BRD in induced-disease models[84]. As this immunostimulant product is relatively new to the commercial market, experiences under typical conditions are somewhat limited. The product did not negatively affect growth or feeding behavior in one study[85]. In a different study evaluating the health and performance effects of the immunostimulant in combination with delayed vaccination and antimicrobial use for control on arrival, this immunostimulant tended to reduce BRD mortality over the entire feeding period[86].

Another alternative that holds potential to replace or reduce the use of traditional antimicrobial therapy is utilizing genetic technology to increase disease resistance of the host animal. One report has suggested that while the overall heritability of BRD is low, the estimates of heritability were higher as disease incidence increased[87]. Results of studies from a USDA – CAP grant identified the specific loci associated with host susceptibility to bovine respiratory disease[88]. While this approach is promising, a genetic test for pneumonia susceptibility is not currently available to cattle producers. Alternatively, but even further from commercialization, is the possibility of using transgenic technology to develop disease resistant cattle. This approach was used to develop dairy cattle that express lysostaphin (an antimicrobial peptide) in the milk to resist *Staphylococcus aureus* infection[89]; however, the development (and consumer acceptance) of transgenic beef to resist pneumonia is not likely in the near future.

Bovine respiratory disease is the most significant disease affecting cattle health and production in the United States. Until effective alternatives to antimicrobials can be developed, approved and commercialized, antimicrobial therapy will be essential to treat these bacterial infections. The differences in cattle production settings and presence or absence of inciting risk factors create many unique situations in which pneumonia can develop. Any label-specified duration of therapy should address the complex, and different, situations in which this disease may be encountered.

[4] Zelnate®, Bayer HealthCare, Shawnee Mission, KS

Pros / Cons of a Defined Duration of Use

While a label-defined duration of use could be beneficial in providing guidance for prescribing veterinarians as to the dosing duration that maximizes therapeutic efficacy for anaplasmosis, bacterial enteritis, liver abscesses and pneumonia and might also minimize the development of antimicrobial resistance for both target pathogens and zoonotic commensal bacteria, the specified duration must be firmly established by the findings of clinical research and pharmacokinetic studies. Any science-based label duration should also be appropriately worded to address the variety of cattle production systems and situations in which these products are used without risk to animal health and welfare.

The disadvantage to imposing a label-defined duration is that there is very little scientific evidence to support specific durations of therapy that minimize the development of antimicrobial resistance in either veterinary or human medical literature. Some of those studies are summarized here to highlight the paucity of data available to producers, veterinary practitioners and pharmaceutical manufacturers regarding optimal durations of antimicrobial therapy.

In a meta-analysis of randomized clinical trials (RCTs) comparing short-course to long-course antimicrobial therapy for acute pyelonephritis in humans, there were no significant differences in efficacy or safety outcome between short- and long-courses of therapy, suggesting that shorter courses could be used without negatively impacting patient outcome[90]. However, there were only 4 RCTs that met the criteria for inclusion in the meta-analysis. Unfortunately, there was significant heterogeneity within the RCTs as the antimicrobials studied and definition of short and long courses were different among the 4 trials; thus, failing to identify an optimal duration for a specific antimicrobial, leading only to the conclusion that there was no significant difference between short and long courses of therapy. Similar meta-analyses of acute bacterial sinusitis[91] and community-acquired pneumonia[92,93] have led to similar conclusions and are constrained by similar study limitations. But not all clinical trials support the use of shorter durations of therapy. Hoberman, *et al.* demonstrated that treating otitis media in young children for 5 days vs. 10 days resulted in higher rates of clinical failure with no significant reduction on the emergence of antimicrobial resistance[94].

Using an *in vitro* infection model, researchers evaluated the effects of both exposure and duration of therapy on the emergence of an antimicrobial resistant population of *Staphylococcus aureus* during therapy with a fluoroquinolone (garenoxicin)[95]. In this study, both low exposure (AUC:MIC=100) and high exposure (AUC:MIC=280) dosing regimens led to a reduction in the total bacterial population from days 0 through 5. However, after day 5, the high dose regimen continued to reduce the total population of *Staphylococcus aureus* in the culture system, while regrowth was seen in the low dose regimen between days 5 through 10. Further analysis of the late stage growth in the low dose regimen confirmed the presence of efflux-pump mediated antimicrobial resistance. From this study, the authors concluded that if low exposure dosing regimens were used, a shorter duration (96 hrs) would minimize the selection of resistant

organisms. Whether this recommendation would or would not apply to other antimicrobials and bacterial organisms has yet to be determined.

In veterinary medicine, the literature to support an optimal duration of antimicrobial exposure is equally scarce. In one study, researchers compared the effectiveness of 1 day versus 4 consecutive days of antimicrobial therapy in reducing surgical site infections of calves undergoing umbilical hernia repair[96]. In this study, calves receiving the longer duration (4 day) antimicrobial regimen had significantly fewer surgical infections. In contrast, a study evaluating 3 day versus 5 day post-surgical antibiotic regimens for horses undergoing exploratory celiotomy found no statistical difference in the occurrence of incisional infections; thus concluding that the longer duration of therapy was not beneficial[97]. Westropp *et al.* compared a traditional, 14 day regimen of amoxicillin-clavulanic acid to a 3 day regimen of enrofloxacin for treating uncomplicated urinary tract infections in dogs[98]. Although duration of therapy was confounded by antimicrobial class in this study, the authors were able to demonstrate non-inferiority of the shorter duration of therapy. While direct comparisons of studies with different host species, disease indications and antimicrobials are of limited value, this comparison highlights the difficulty of assigning a defined duration of therapy to adequately address the variety of production systems in beef and dairy operations.

While these studies generally support shorter durations of therapy, information to support a specific duration of therapy for anaplasmosis, enteritis, liver abscesses and pneumonia is currently lacking. Given the in-feed administration of some of these products, any extra label use (including off label duration) is strictly prohibited, therefore a specified label duration must be explicitly followed. Furthermore, as of 1 January 2017, any use requires authorization by a licensed veterinarian through a veterinary feed directive (VFD) order. In keeping with the requirements for VFD expiration and a valid veterinary-client-patient relationship, the need for continued administration of these products in a specific herd will be re-evaluated by the veterinarian of record every 6 months, at minimum, or as dictated by the product labeling.

Again, we appreciate the opportunity to comment and believe that assigning specific durations of therapy for these drugs and indications in cattle, as found in Table 1 of the *Federal Register* notice, raise additional concerns that warrant consideration. Specifically:

- Will defined durations of use create unintended consequences for stakeholders and their animals by limiting the professional judgement of the prescribing veterinarian, who is tasked with the oversight of antimicrobial drugs?
- Does current research support science-based, universal durations of use for all situations described in this notice for information?
- If so, does that research support the ability of altered durations to also subsequently mitigate antimicrobial resistance?

- What are the complicating factors and can these factors be mitigated for defined durations of use?
- If an optimal duration of therapy represents a compromise between clinical efficacy and mitigation of antimicrobial resistance, what does the agency deem an acceptable decrease in clinical efficacy to justify a decrease in duration of therapy?
- Ultimately, will the health and well-being of cattle be compromised by more prescriptive actions to define durations of use?

In summary, the NCBA and the undersigned organizations believe that in the absence of specific, science-based durations of therapy for these particular diseases, risk factors such as: vector season length for anaplasmosis, immune status and inclement weather patterns for bacterial enteritis, ration management for liver abscesses, and transportation and commingling for pneumonia, become extremely important considerations for assigning an extended (or shortened) duration of therapy and that flexibility to consider these factors is paramount. Our concerns for scientific evidence to support changes in labeling are shared by the Chairman of the U.S. Senate Committee on Agriculture, Nutrition, and Forestry, Senator Pat Roberts, and the Chairman of the U.S. Senate Committee on Health, Education, Labor, and Pensions, Senator Lamar Alexander, in a December 2016 letter to FDA Commissioner, Robert M. Califf. We have attached the letter as an addendum to our comments. Furthermore, the NCBA believes that the use of antimicrobials for these diseases in cattle meets the criteria of appropriate preventive use in that: there is evidence of efficacy, the use is consistent with accepted veterinary practice, the use addresses a particular pathogen, and there are no currently available or effective alternatives to antibiotics. Furthermore, ***only*** the veterinarian of record, who is familiar with a specific cattle operation, is positioned to determine the most appropriate duration of antimicrobial therapy for a specific group of animals, based on an assessment of disease risk. Thus, in keeping with the FDA's mission to protect both human and animal health, we believe that any regulatory steps taken should support the professional judgement and experience of our veterinarians and ensure the health and well-being of our cattle, and ultimately, the safety of the nation's beef supply. As producers and veterinarians, we recognize that the judicious use of these antimicrobial drugs is necessary to protect their efficacy, and we strive to continue to refine our production practices and find antibiotic alternatives which will lessen their requirements for use.

We appreciate the opportunity to provide information and look forward to working with the agency on the issues and questions raised in our comments. If you have any questions or concerns, please contact Dr. Kathy Simmons, NCBA's Chief Veterinarian, at 202-347-0228 or at ksimmons@beef.org.

Respectfully submitted,

Craig Uden

President, National Cattlemen's Beef Association

Tom Portillo, DVM

President, Academy of Veterinary Consultants

K. Fred Gingrich, II, DVM

Executive Vice President, American Association of Bovine Practitioners

Jim Mulhern

President & CEO, National Milk Producers Federation

CITED REFERENCES

[1] Lee TL, Thomson DU. 2016. A survey to describe beef producer opinions on antibiotic use and consumer perceptions of antibiotics in the beef industry. The Bovine Practitioner 50: 54-59.
[2] Antibiotic Stewardship for Beef Producers. Available at: http://www.bqa.org/Media/BQA/Docs/bqa_antibiotics_final.pdf Accessed: 25 January 2017.
[3]National Dairy FARM Milk and Dairy Beef Drug Residue Prevention Reference Manual. Available at http://www.nationaldairyfarm.com/sites/default/files/2016-Residue-Manual.pdf. Accessed February 28, 2017.
[4] National Dairy FARM Animal Care Reference Manual. Available at http://www.nationaldairyfarm.com/sites/default/files/Version-3-Manual.pdf. Accessed February 28, 2017.
[5] The Beef Checkoff. 2011 National Beef Quality Audit. Available at: http://www.bqa.org/Media/BQA/Docs/nbqa_significant_findings.pdf Accessed: 27 January 2017.
[6] U.S. Food and Drug Administration. Available at: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf Accessed: 15 January 2017.
[7] Executive Office of the President – President's Council of Advisors on Science and Technology. Available at: https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf ; pg. 53. Accessed: 15 January 2017.
[8] U.S. Food and Drug Administration. Available at: http://www.fda.gov/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216939.htm#question6 Accessed: 15 January 2017.
[9] Seal BS, Lillehoj HS, Donovan DM, Gay CG. 2013. Alternatives to antibiotics: a symposium on the challenges and solutions for animal production. Animal Health Research Reviews 14: 78-87.
[10] OIE. 2015. Chapter 2.4.1: bovine anaplasmosis. In: Manual of standards for diagnostic tests and vaccines for terrestrial animals. Available at: http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.04.01_BOVINE_ANAPLASMOSIS.pdf Accessed: 14 Nov 2016.
[11] Aubry P, Geale DW. 2011. A review of bovine anaplasmosis. Transboundary and Emerging Diseases 58: 1-30.
[12] Kocan KM, de la Fuente J, Blouin EF, Garcia-Garcia JC. 2004. *Anaplasma marginale* (Rickettsiales: Anaplasmataceae): recent advances in defining host-pathogen adaptations of a tick-borne rickettsia. Parasitology 129: S285-300.
[13] Kocan KM, de la Fuente J, Cabezas-Cruz A. 2015. The genus *Anaplasma*: new challenges after reclassification. Revue Scientifique et Technique (International Office of Epizootics) 34: 577-586.
[14] Kocan KM, de la Fuente J, Guglielmone AA, Melendez RD. 2003. Antigens and alternatives for control of *Anaplasma marginale* infection in cattle. Clinical Microbiology Reviews 16: 698-712.
[15] Kocan KM, de la Fuente J, Blouin EF, Coetzee JF, Ewing SA. 2010. The natural history of *Anaplasma marginale*. Veterinary Parasitology 167: 95-107.
[16] Reeves JD, Swift BL. 1977. Iatrogenic transmission of *Anaplasma marginale* in beef cattle. Vet Med Small Anim Clin 72: 911-912.
[17] Reinbold JB, Coetzee JF, Hollis LC, Nickell JS, Riegel CM, Christopher JA, Ganta RR. 2010. Comparison of iatrogenic transmission of *Anaplasma marginale* in Holstein steers via needle and needle-free injection techniques. American Journal of Veterinary Research 71: 1178-1188.
[18] U.S. Food and Drug Administration. Available at: https://animaldrugsatfda.fda.gov/adafda/views/#/search. Accessed: 14 Nov 2016.
[19] Coetzee JF, Apley MD, Kocan KM, Rurangirwa FR, Van Donkersgoed J. 2005. Comparison of three oxytetracycline regimens for the treatment of persistent *Anaplasma marginale* infections in beef cattle. Veterinary Parasitology 127: 61-73.

[20] Coetzee JF. 2007. Treatment of persistent *Anaplasma marginale* infections with oral chlortetracycline. Proceedings of the North American Veterinary Conference.
[21] Available at: http://www.interchemie.com/veterinary-medicines/imochem-120.html Accessed: 16 November 2016
[22] McHardy N, Berger J, Taylor RJ, Farebrother D, James JA. 1980. Comparison of gloxazone, an effective but toxic anaplasmacide, with imidocarb dihydrochloride. Research in Veterinary Science 29: 198-202.
[23] Jonsson N, Reid SWJ. 2000. Global climate change and vector borne diseases. The Veterinary Journal 160: 87-89.
[24] Hanzlicek GA, Raghavan RK, Ganta RR, Anderson GA. 2016. Bayesian space-time patterns and climatic determinants of bovine anaplasmosis. PlosONE DOI: 10.1371/journal.pone.0151924
[25] Kocan KM, Blouin EF, Barbet AF. 2000. Anaplasmosis Control: Past, Present, and Future. Annals of the New York Academy of Sciences 916 (Tropical Veterinary Diseases: Control and Prevention in the Context of the New World Order): 501-509.
[26] De Waal DT. 2000. Anaplasmosis Control and Diagnosis in South Africa. Annals of the New York Academy of Sciences 916 (Tropical Veterinary Diseases: Control and Prevention in the Context of the New World Order): 474-483.
[27] Uilenberg G. 1990. Present and future possibilities for the control of cowdriosis and anaplasmosis. Veterinary Quarterly 12: 39-45.
[28] United States Department of Agriculture. Prepared October 2016. Veterinary Biological Products. Accessed 13 October 2016 at: https://www.aphis.usda.gov/animal_health/vet_biologics/publications/CurrentProdCodeBook.pdf
[29] Kuttler KL, Zaugg JL, Johnson LW. 1984. Serologic and clinical responses of premunzied, vaccinated and previously infected cattle to challenge exposure by two different *Anaplasma marginale*. American Journal of Veterinary Research 45: 2223-2226.
[30] De la Fuente J, Almazan C, Canales M, de la Lastra JMP, Kocan KM, Willadsen P. 2007. A ten-year review of commercial vaccine performance for control of tick infestations on cattle. Animal Health Research Reviews 8: 23-28.
[31] Fosgate GT, Urdaz-Rodriguez JH, Dunbar MD, Rae DO, Donovan GA, Melendez P, Dobek GL, Alleman AR. 2010. Diagnostic accuracy of methods for detecting *Anaplasma marginale* infection in lactating dairy cattle of Puerto Rico. Journal of Veterinary Diagnostic Investigation 22: 192-199.
[32] U.S. Department of Agriculture – Animal and Plant Health Inspection Service. 2010. Beef 2007-08 Part V: Reference of beef cow-calf management practices in the United States, 2007-08. Available at: https://www.aphis.usda.gov/animal_health/nahms/beefcowcalf/downloads/beef0708/Beef0708_dr_PartV.pdf Accessed: 17 November 2016.
[33] Smith BP (editor). 1996. Large Animal Internal Medicine (2nd ed.). Mosby-Year Book, Inc. St. Louis, MO.
[34] Janke BH, Francis DH, Collins JE, Libal MC, Zeman DH, Johnson DD. 1989. Attaching and effacing *Escherichia coli* infections in calves, pigs, lambs and dogs. Journal of Veterinary Diagnostic Investigation 1: 6-11.
[35] Younaes YD, Herdt TH. 1987. Changes in small intestinal morphology and flora associated with decreased energy digestibility in calves with naturally occurring diarrhea. American Journal of Veterinary Research 48: 719-725.
[36] Smith GW. 2013. Antibiotic decision making – calf scours. Proceedings of the American Association of Bovine Practitioners 46: 65-70.
[37] Holland RD. 1990. Some infectious causes of diarrhea in young farm animals. Clinical Microbiology Reviews 3: 345-375.
[38] Nagy B, Fekete PZ. 2005. Enterotoxigenic *Escherichia coli* in veterinary medicine. International Journal of Medical Microbiology 295: 443-454.
[39] Smith G. 2015. Antimicrobial decision making for enteric diseases of cattle. Veterinary Clinics of North America: Food Animal Practice 31:47-60.

[40] Haggard DL. 1985. Bovine enteric colibacillosis. The Veterinary Clinics of North America: Food Animal Practice 1: 495-508.
[41] Acres SD, Isaacson RE, Babiuk LA, Kapitany RA. 1979. Immunization of calves against enterotoxigenic colibacillosis by vaccinating dams with purified K99 antigen and whole cell bacterins. Infection and Immunity 25: 121-126.
[42] Sherman DM, Acres SD, Sadowski PL, Springer JA, Bray B, Raybould TJG, Muscoplat CC. 1983. Protection of calves against fatal enteric colibacillosis by orally administered *Escherichia coli* K99-Specific monoclonal antibody. Infection and Immunity 42: 653-658.
[43] Smith W, Huggins MB. 1983. Effectiveness of phages in treating experimental *Escherichia coli* diarrhea in calves, piglets and lambs. Journal of General Microbiology 129: 2659-2675.
[44] Barrow P, Lovell M, Berchieri A. 1998. Use of lytic bacteriophage for control of experimental *Escherichia coli* septicemia and meningitis in chickens and calves. Clinical and Diagnostic Laboratory Immunology 5: 294-298.
[45] Johnson RP, Gyles CL, Huff WE, Ojha S, Huff GR, Rath NC, Donoghue AM. 2008. Bacteriophages for prophylaxis and therapy in cattle, poultry and pigs. Animal Health Research Reviews 9: 201-215.
[46] Szkaradkiewicz AK, Karpinski TM. 2013. Probiotics and prebiotics. Journal of Biology and Earth Sciences 3: M42-M47.
[47] Callaway TR, Edrington TS, Anderson RC, Harvey RB, Genovese KJ, Kennedy CN, Venn DW, Nisbet DJ. 2008. Probiotics, prebiotics and competitive exclusion for prophylaxis against bacterial disease. Animal Health Research Reviews 9: 217-225.
[48] Clements ML, Levine MM, Black RE, Rovins-Browne RM, Cisneros LA, Drusano GL, Lanata CF, Saah AJ. 1981. *Lactobacillus* prophylaxis for diarrhea due to enterotoxigenic *Escherichia coli.* Antimicrobial Agents and Chemotherapy 20: 104-108.
[49] Otero MC, Morelli L, Nader-Macias ME. 2006. Probiotic properties of vaginal lactic acid bacteria to prevent metritis in cattle. Letters in Applied Microbiology 43: 91-97.
[50] Smith HA. 1944. Ulcerative lesions of the bovine rumen and their possible relation to hepatic abscesses. American Journal of Veterinary Research 5: 234-242.
[51] Rezac DJ, Thomson DU, Bartle SJ, Osterstock JB, Prouty FL, Reinhardt CD. 2014. Prevalence, severity, and relationships of lung lesions, liver abnormalities and rumen health scores measured at slaughter in beef cattle. Journal of Animal Science 92: 2595-2602.
[52] Tadepalli S, Narayanan SK, Stewart GC, Chengappa MM, Nagaraja TG. 2009. *Fusobacterium necrophorum:* A ruminal bacterium that invades liver to cause abscesses in cattle. Anaerobe 15: 36-43.
[53] Amachawadi RG, Nagaraja TG. 2016. Liver abscesses in cattle: A review of incidence in Holsteins and of bacteriology and vaccine approaches to control in feedlot cattle. Journal of Animal Science 94: 1620-1632.
[54] McKeith RO, Gray GD, Hale DS, Kerth CR, Griffin DB, Savell JW, Raines CR, Belk KE, Woerner DR, Tatum JD, Igo JL, VanOverbeke DL, Mafi GG, Lawrence TE, Delmore RJ, Christensen LM, Shackelford SD, King DA, Wheeler TL, Meadows LR, O'Connor ME. 2012. National Beef Quality Audit-2011: Harvest-floor assessments of targeted characteristics that affect quality and value of cattle, carcasses, and byproducts. Journal of Animal Science 90: 5135-5142.
[55] Nagaraja TG, Lechtenberg KF. 2007. Liver abscesses in feedlot cattle. The Veterinary Clinics of North America: Food Animal Practice 23: 351-369.
[56] Vogel GJ, Laudert SB. 1994. The influence of Tylan on liver abscess control and animal performance. Journal of Animal Science 72: 293.
[57] Brown H, Bing RF, Grueter HP, McAskill JW, Cooley CO, Rathmacher RP. 1975. Tylosin and chlortetracycline for the prevention of liver abscesses, improved weight gains and feed efficiency in feedlot cattle. Journal of Animal Science 40: 207-213.
[58] Rogers JA, Branine ME, Miller CR, Wray MI, Bartle SJ, Preston RL, Gill DR, Pritchard RH, Stilborn RP, Bechtol DT. 1995. Effects of dietary virginiamycin on performance and liver abscess incidence in feedlot cattle. Journal of Animal Science 73: 9-20.

[59] Meyer NF, Erickson GE, Klopfenstein TJ, Greenquist MA, Luebbe MK, Williams P, Engstrom MA. 2014. Effect of essential oils, tylosin, and monensin on finishing steer performance, carcass characteristics, liver abscesses, ruminal fermentation, and digestibility. Journal of Animal Science 87: 2346-2354.
[60] Montgomery JL. 2007. Method of feeding the cattle with feed additives that increases beef production and reduces liver abscess. U.S Patent 7207289 B2, filed 20 May 2005, and published 24 April 2007.
[61] Saginala S, Nagaraja TG, Lechtenberg KF, Chengappa MM, Kemp KE, Hine PM. 1997. Effect of *Fusobacterium necrophorum* leukotoxoid vaccine on susceptibility to experimentally induced liver abscesses in cattle. Journal of Animal Science 75: 1160-1166.
[62] Jones G, Jayappa H, Hunsaker B, Sweeney D, Rapp-Gabrielson V, Wasmoen T, Nagaraja TG, Swingle S, Branine M. 2004. Efficacy of an *Arcanobacterium pyogenes – Fusobacterium necrophorum* bacterin-toxoid as an aid in the prevention of liver abscesses in feedlot cattle. The Bovine Practitioner 38: 36-44.
[63] Fox JT, Thomson DU, Lindberg NN, Barling K. 2009. A comparison of two vaccines to reduce liver abscesses in natural-fed beef cattle. The Bovine Practitioner 43: 168-174.
[64] Nagaraja TG, Chengappa MM. 1998. Liver abscesses in feedlot cattle: a review. Journal of Animal Science 76: 287-298.
[65] Reinhardt CD, Hubbert ME. 2015. Control of liver abscesses in feedlot cattle: A review. The Professional Animal Scientist 31: 101-108.
[66] U.S. Department of Agriculture – Animal and Plant Health Inspection Service. 2011. Feedlot 2011 Part IV: Health and health management on U.S. feedlots with a capacity of 1,000 or more head. Available at: https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartIV.pdf Accessed: 2 December 2016.
[67] U.S. Department of Agriculture – Animal and Plant Health Inspection Service. 2007. Dairy 2007 Part III: Reference of dairy cattle health and management practices in the United States, 2007. Available at: https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy07/Dairy07_dr_PartIII_rev.pdf Accessed: 2 December 2016.
[68] Cusack PMV, McMeniman N, Lean IJ. 2003. The medicine and epidemiology of bovine respiratory disease in feedlots. Australian Veterinary Journal 81: 480-487.
[69] Griffin D, Chengappa MM, Kuszak J, McVey DS. 2010. Bacterial pathogens of the bovine respiratory disease complex. The Veterinary Clinics of North America: Food Animal Practice 26: 381-394.
[70] Wittum TE, Woollen NE, Perino LJ, Littledike ET. 1996. Relationships among treatment for respiratory tract disease, pulmonary lesions evident at slaughter, and rate of weight gain in feedlot cattle. Journal of the American Veterinary Medical Association 15: 814-818.
[71] White BJ, Renter DG. 2009. Bayesian estimation of the performance of clinical observations and harvest lung scores for diagnosing bovine respiratory disease in post-weaned beef calves. Journal of Veterinary Diagnostic Investigation 21: 446-453.
[72] Dabo SM, Taylor JD, Confer AW. 2008. *Pasteurella multocida* and bovine respiratory disease. Animal Health Research Reviews 8: 129-150.
[73] Gallo GF, Berg JL. 1995. Efficacy of a feed-additive antibacterial combination for improving feedlot cattle performance and health. Canadian Veterinary Journal 36: 223-229.
[74] Agga GE, Schmidt JW, Arthur TM. 2016. Effects of in-feed chlortetracycline prophylaxis in beef cattle on animal health and antimicrobial-resistant *Escherichia coli*. Appl Environ Microbiol 82:7197–7204.
[75] Theurer ME, Larson RL, White BJ. 2015. Systematic review and meta-analysis of the effectiveness of commercially available vaccines against bovine herpesvirus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza type 3 virus for mitigation of bovine respiratory disease complex in cattle. Journal of the American Veterinary Medical Association 246: 126-142.
[76] U.S. Department of Agriculture – Animal and Plant Health Inspection Service. 2011. Feedlot 2011 Part I: Management practices on U.S. feedlots with a capacity of 1,000 or more head. Available at:

https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartI.pdf Accessed: 2 December 2016.
[77] U.S. Department of Agriculture – Animal and Plant Health Inspection Service. 2011. Feedlot 2011 Part II: Management practices on U.S. feedlots with a capacity of fewer than 1,000. Available at: https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartII.pdf Accessed: 2 December 2016.
[78] Murray GM, O'Neill RG, More SJ, McElroy MC, Earley B, Cassidy JP. 2016. Evolving views on bovine respiratory disease: An appraisal of selected control measures – Part 2. The Veterinary Journal 217: 78-82.
[79] U.S. Department of Agriculture – Animal and Plant Health Inspection Service. 2007. Dairy 2007 Part I: Reference of dairy cattle health and management practices in the United States. Available at: https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy07/Dairy07_dr_PartI.pdf Accessed: 26 January 2017.
[80] Rice JA, Carrasco-Medina L, Hodgins DC, Shewen PE. 2008. *Mannheimia haemolytica* and bovine respiratory disease. Animal Health Research Reviews 8: 117-128.
[81] Bateman KG. 1988. Efficacy of a pasteurella haemolytica vaccine/bacterial extract in the prevention of bovine respiratory disease in recently shipped feedlot calves. The Canadian Veterinary Journal 29: 838-839.
[82] Larson RL, Step DL. 2012. Evidence based effectiveness of vaccination against *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* in feedlot cattle for mitigating the incidence and effect of bovine respiratory disease complex. Veterinary Clinics of North America – Food Animal Practice 28: 97-106.
[83] Larson RL, Step DL. 2012. Evidence-based effectiveness of vaccination against Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in feedlot cattle for mitigating the incidence and effect of bovine respiratory disease complex. Veterinary Clinics of North America: Food Animal Practice 28: 97 – 106.
[84] Zelnate product label. Available at: https://bayer.naccvp.com/product/basic/view/1040158?e=LSdew7K4HnVeeL2EuzyjnfL5DhrACqQQ Accessed: 13 December 2016.
[85] Gaspers JJ, Swanson KC, Keomanivong FE, Fontoura ABP, Ward AK, Knutson E, Stokka G. 2016. Evaluation of response to vaccination with a bacterial-plasmid DNA, Zelnate, on feedlot performance of weaned calves. 2016 North Dakota Beef Report. Available at: https://www.researchgate.net/profile/Ananda_Fontoura/publication/308404062_Evaluation_of_response_to_vaccination_with_a_bacterial-produced_plasmid_DNA_Zelnate_on_feedlot_performance_of_weaned_calves/links/57e2f16b08aecd0198dd82fc.pdf Accessed: 13 Dec 2016.
[86] Rogers KC, Miles DG, Renter DG, Sears JE, Woodruff JL. 2016. Effects of delayed respiratory viral vaccine and/or inclusion of an immunostimulant on feedlot health, performance, and carcass merits of auction-market derived feeder heifers. The Bovine Practitioner 50: 154- 162.
[87] Snowder GD, Van Vleck LD, Cundiff LV, Bennett GL. 2005. Influence of breed, heterozygosity, and disease incidence on estimates of variance components of respiratory disease in preweaned beef calves. Journal of Animal Science 83: 1247-1261.
[88] Neupane M, Kiser JN, Seabury CM, Taylor JF, Womack JE, BRD-CAP team, Neibergs HL. 2015. Genetic approaches to identify genomic regions associated with decreased susceptibility to bovine respiratory disease complex. Proceedings of the American Association of Bovine Practitioners Annual Conference 48: 148-153.
[89] Donovan DM, Kerr DE, Wall RJ. 2005. Engineering disease resistant cattle. Transgenic Research 14: 563-567.
[90] Kyriakidou KG, Rafailidis P, Matthaiou DK, Athanasiou S, Falagas ME. 2008. Short- versus long-course antibiotic therapy for acute pyelonephritis in adolescents and adults: a meta-analysis of randomized clinical trials. Clinical Therapeutics 30: 1859-1868.

[91] Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK, 2009. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. British Journal of Clinical Pharmacology 67: 161-171.
[92] Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos AP, Athanassa Z, Falagas ME, 2008. Short- versus long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. Drugs 68: 1841-1854.
[93] Li JZ, Winston LG, Moore DH, Bent S, 2007. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. The American Journal of Medicine 120: 783-790.
[94] Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, Martin JM, Kurs-Lasky M, Copelli SJ, Colborn K, Block SL, Labella JJ, Lynch TG, Cohen NL, Haralam M, Pope MA, Nagg JP, Green JD, Shaikh N. 2016. Shortened antimicrobial treatment for acute otitis media in young children. The New England Journal of Medicine 375: 2446-2456.
[95] Tam VH, Louie A, Fritsche TR, Deziel M, Liu W, Brown DL, Deshpande L, Leary R, Jones RN, Drusano GL, 2007. Impact of drug-exposure intensity and duration of therapy on the emergence of *Staphylococcus aureus* resistance to a quinolone antimicrobial. The Journal of Infectious Diseases 195: 1818-1827.
[96] Klein WR, Firth EC. 1988. Infection rates in contaminated surgical procedures: a comparison of prophylactic treatment for one day or four days. Veterinary Record 123: 564-566.
[97] Durward-Akhurst SA, Mair TS, Boston R, Dunkel B. 2013. A comparison of two antimicrobial regimens on the prevalence of incisional infections after colic surgery. Veterinary Record 172.
[98] Westropp JL, Sykes JE, Irom S, Daniels JB, Smith A, Keil D, Settje T, Wang Y, Chew DJ. 2012. Evaluation of the efficacy and safety of high dose short duration enrofloxacin treatment regimen for uncomplicated urinary tract infections in dogs. Journal of Veterinary Internal Medicine 26: 506-512.

ADDENDUM TO COMMENTS FOR **FDA-2016-D-2635, THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS; ESTABLISHING APPROPRIATE DURATIONS OF THERAPEUTIC ADMINISTRATION; REQUEST FOR COMMENTS**

NATIONAL CATTLEMEN'S BEEF ASSOCIATION; ACADEMY OF VETERINARY CONSULTANTS; AMERICAN ASSOCIATION OF BOVINE PRACTITIONERS; NATIONAL MILK PRODUCERS FEDERATION

MARCH 13, 2017

CONTENTS:

United States Senate

WASHINGTON, DC 20510

December 6, 2016

The Honorable Robert M. Califf
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Califf:

We write regarding the recent notice by the U.S. Food and Drug Administration (FDA) seeking public comment on, "The Judicious Use of Medically Important Antimicrobial Drugs in Food Producing Animal; Establishing Appropriate Duration of Therapeutic Administration," to express concern and urge you to ensure that any guidance or regulations are based on scientific evidence. Specifically, we ask you to heed input from the agriculture sector given the widespread effect changes to current practice could have on animal health and welfare. The U.S. livestock and poultry sectors understand the importance of targeted and judicious antimicrobial use in agriculture to help address antimicrobial resistance in humans. American farmers and ranchers implement practices to minimize animal disease threats, which protect animal welfare and ensure the safety of our nation's food supply. This commitment is demonstrated by the cooperative role farmers, ranchers, animal drug manufacturers, and veterinarians have played as FDA has begun implementing Guidance 209 and Guidance 213, which prevent the use of medically important antimicrobials for growth promotion purposes and require all remaining antimicrobial drugs be prescribed by a veterinarian.

We have heard from many of our constituents that FDA's recent action gives little consideration for the effectiveness of Guidances 209 and 213, which have only recently begun to be incorporated into current practices. For example, the deadline for changes to the marketing status of antimicrobial drugs from over-the-counter to either prescription or veterinary feed directive status is January 1, 2017. As FDA's efforts have yet to be fully implemented, we are concerned that the agency is already proposing additional actions before knowing the full effect of its initial guidance documents. We hope that the agency will take the appropriate steps to determine the effectiveness of its current regulations and guidance policies, and ensure there are metrics in place to analyze trends in antimicrobial resistance before implementing additional requirements.

Importantly, some of the dosages listed in the agency's recent proposal have no alternative medicines that could be used as a substitute. This void could force widespread change in livestock and poultry diets, which are determined by a precise science. It's important that the agency gives careful consideration to the effects this proposal could have across American agriculture. While we share the agency's concerns regarding antimicrobial resistance, as it is a complex phenomenon, it is critical that proposed changes to agricultural and animal health practices are based on scientific evidence. Without such scientific evidence, farmers and ranchers could be making widespread and costly changes that have little to no impact on antimicrobial resistance trends while jeopardizing animal health and welfare.

It is with this background that we urge the agency to base regulatory changes on scientific evidence and consider the widespread effects arbitrary changes could have on public health, animal health and animal welfare. As evidenced by the agency's recent extension of the comment period for this notice, this is a complex issue which deserves careful deliberation based on available science. We thank you in advance for your consideration of this request and appreciate your continued efforts to protect public health and animal health.

Sincerely,

Pat Roberts, Chairman
U.S. Senate Committee on Agriculture,
Nutrition, and Forestry

Lamar Alexander, Chairman
U.S. Senate Committee on Health,
Education, Labor, and Pensions