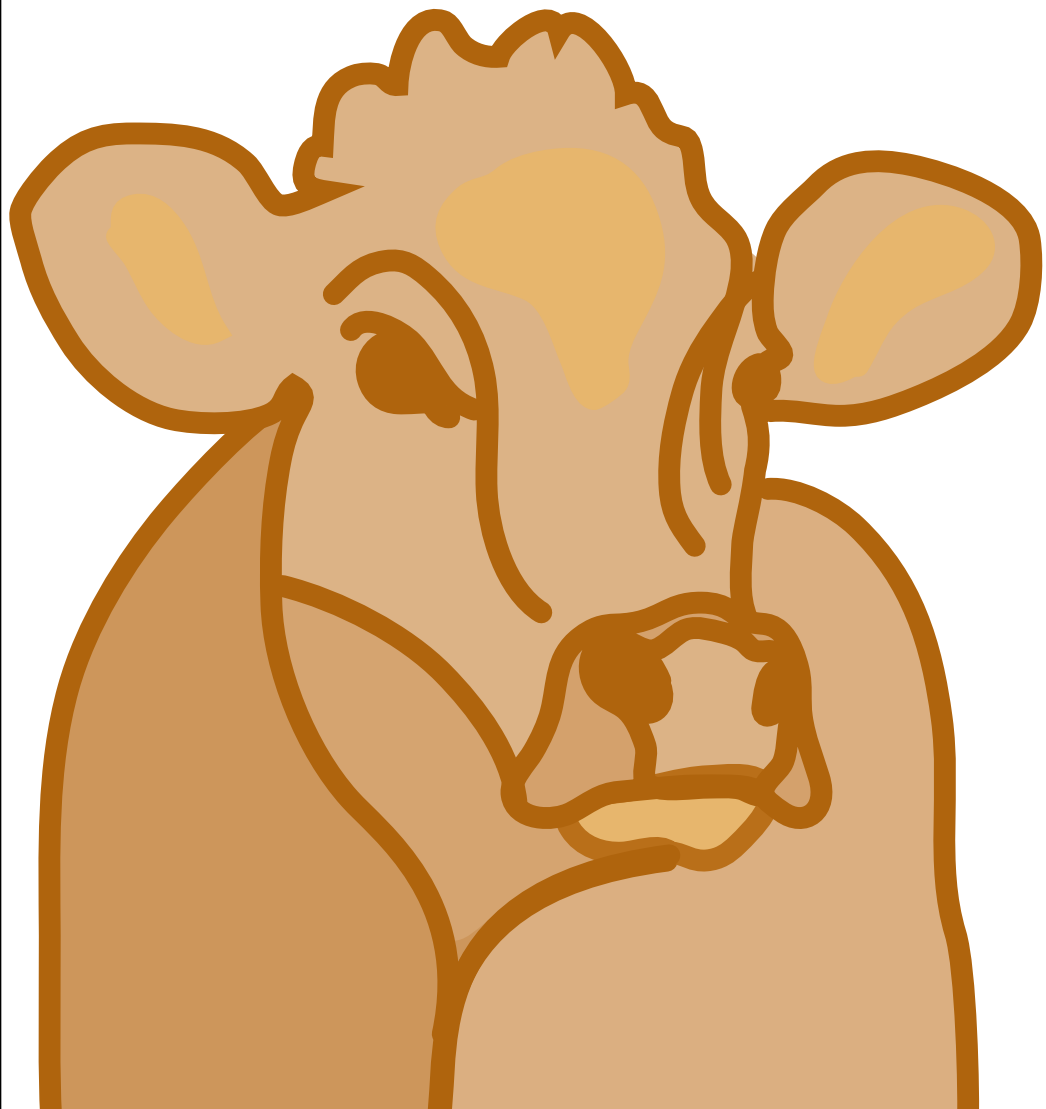


Judicious Use of Antimicrobials for
Dairy Cattle
Veterinarians





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INTRODUCTION

Antimicrobials are needed for the relief of pain and suffering in animals. For food animals, the gains that have been made in food production capacity would not have been possible without the ability of safe and effective drugs to contain the threat of disease to animals. The increased capacity of the United States livestock and poultry producer has kept high quality protein available and affordable for the majority of consumers in the U.S. and other countries. The World Health Organization stated, "Antimicrobials are vital medicines for the treatment of bacterial infections in both humans and animals. Antimicrobials have also proved to be important for sustainable livestock production and for the control of animal infections that could be passed on to humans." The report by the National Research Council and Institute of Medicine states: "The benefit to human health in the proper use of antibiotics in food animals is related to the ability for these drugs to combat infectious bacteria that can be transferred to humans by either direct contact with the sick animal, consumption of food contaminated with pathogens from animals, or proliferation into the environment." However, the use of antimicrobials in food animals is not without risk.

In recent years, concerns about the use of antimicrobial products in food-producing animals have focused on human food safety because foods of animal origin are sometimes identified as the vehicles of food borne disease in humans and, therefore, also vehicles of resistant food borne pathogens and resistant genetic material. The major zoonotic pathogens of concern for the development of antimicrobial resistance are *Salmonella* spp. and *Campylobacter jejuni*. A recent report estimated that 80% of the estimated 2.5 million annual human cases in the United States of campylobacteriosis are food borne and that 95% of the 1.4 million annual human cases of nontyphoidal salmonellosis are food borne. This equates to 1.96 million cases of food borne campylobacteriosis and 1.34 million cases of food borne salmonellosis per year in the United States. If a significant percentage of *Salmonella* or *Campylobacter* become resistant to the antibiotics used to treat those infections in humans, there could be a significant impact on human health.

Resistance to antimicrobials existed even before antimicrobials were used. However, this intrinsic form of resistance is not a major source of concern for human and animal health. The vast majority of drug-resistant organisms have instead emerged as a result of genetic changes, acquired through mutation or

transfer of genetic material during the life of the microorganisms, and subsequent selection processes. Mutational resistance develops as a result of spontaneous mutation in a locus on the microbial chromosome that controls susceptibility to a given antimicrobial. The presence of the drug serves as a selecting mechanism to suppress susceptible microorganisms and promote the growth of resistant mutants. Spontaneous mutations are transmissible vertically. Resistance can also develop as a result of transfer of genetic material between bacteria. Plasmids, which are small extra-chromosomal DNA molecules, transposons and integrons, which are short DNA sequences, can be transmitted both vertically and horizontally and can code for multi-resistance. It is believed that a major portion of acquired resistance is plasmid-mediated, although the method of resistance transfer varies for specific drug /bacteria combinations.

Resistance depends on different mechanisms and more than one mechanism may operate for the same antimicrobial. Microorganisms resistant to a certain antimicrobial may also be resistant to other antimicrobials that share a mechanism of action or attachment. Such relationships, known as cross-resistance, exist mainly between agents that are closely related chemically (e.g. neomycin-kanamycin), but may also exist between structurally unrelated chemicals with similar mechanisms of action (e.g. erythromycin- lincomycin). Microorganisms may also be resistant to several unrelated antimicrobials at the same time, even though the mechanisms of resistance may be very different. Use of one such antimicrobial may therefore also select for resistance to the other antimicrobials.

Definitive answers about the safety of antimicrobial use in animals remain scientifically challenging, but more information is accumulating that raises concerns about food safety. As a result of treating animals with antibiotics, food borne microbes may become resistant to the antibiotics used to treat human disease. When an animal is treated with an antimicrobial drug, a selective pressure is applied to all bacteria exposed to the drug. Bacteria that are susceptible to the antimicrobial are killed or put at a competitive disadvantage, while bacteria that have the ability to resist the antimicrobial have an advantage and are able to grow more rapidly than more susceptible bacteria. In addition, bacteria can become resistant when resistance genes are passed from a resistant bacterium to a sensitive one. Thus, antimicrobial agents may increase the prevalence of resistant bacteria among both target pathogens and normal bacterial flora.

For example, despite several restrictions placed on the use of the two approved poultry fluoroquinolone products in the U.S., ciprofloxacin-resistant *Campylobacter* were recently isolated from 20% of domestic retail chicken products sampled. Molecular subtyping revealed an association between resistant *C. jejuni* strains from chicken products and *C. jejuni* strains from domestically acquired human cases of campylobacteriosis. The 1998 Annual Report of the National Antimicrobial Resistance Monitoring System-Enteric Bacteria (NARMS) reported 13.3% of the human *Campylobacter* isolates were resistant to ciprofloxacin. Preliminary data from 1999 reveal an increase to 21% resistance. Temporal relationships between ciprofloxacin-resistant *Campylobacter* and approval of fluoroquinolones for food-producing animals have also been noted in the Netherlands, the United Kingdom, and Spain.

Similarly, a temporal association has been noted between lessened susceptibility to fluoroquinolones among *Salmonella enterica* serotype Typhimurium Definitive Type 104 (DT104) and the approval and use of a fluoroquinolone for veterinary therapeutic use in the United Kingdom. This organism has also been identified in livestock and poultry in the U.S. Human disease caused by DT104 in the U.S. has been associated with consumption of unpasteurized beef products and direct contact with livestock. NARMS has identified small numbers of human *Salmonella* isolates in the U.S. with reduced susceptibility to ciprofloxacin. Although the numbers are small, there is a trend towards reduced susceptibility to ciprofloxacin as measured by the percentage of *Salmonella* isolates with a minimum inhibitory concentration equal to or greater than 0.25 mg/ml. The percentages were 0.4% of the *Salmonella* isolates in 1996 to 0.6% in 1997, 0.7% in 1998, and 1.3% in 1999 (preliminary data as of October 1, 1999).

NARMS also tests *Salmonella* and *Campylobacter* isolates obtained from several species of animals. The isolates come from diagnostic laboratories, healthy animals on farms, and raw products collected at slaughter or processing plants. The *Salmonella* isolates are tested for susceptibility to 17 antimicrobials and the *Campylobacter* isolates are tested for susceptibility to eight antimicrobials. In 1998, resistance of the *Salmonella* isolates was most common to tetracycline (38% of the isolates), sulfamethoxazole (32%), streptomycin (35%), ampicillin (18%), ticarcillin (17%), kanamycin (15%), and gentamicin (11%). Resistance of the *Campylobacter* isolates was most common to tetracycline (60%), nalidixic acid (16%), ciprofloxacin (11%), clindamycin (7%), and azithromycin and erythromycin (6%) each. Resistance to multiple antimicrobials is a concern. As organisms become resistant to more antimicrobials, the problem of therapy is compounded. In 1998, 40% of the animal *Salmonella* isolates were resistant to 2 or more antimicrobials. This is an increase from 25% in 1997. In 1998, 18% were resistant to 5 or more antimicrobials compared to 11% in 1997.

Unfortunately there is not a national monitoring system that tests for resistance in animal pathogens so we are unable to track and report trends.

This document has been prepared to help dairy cattle practitioners in their efforts to use antimicrobials judiciously to minimize the development of resistance in human and animal pathogens while maintaining effectiveness to treat and prevent diseases of food animals.

JUDICIOUS USE

Whenever an animal or human host is exposed to antimicrobials, there will be some degree of selection for a resistant bacterial population. Selection will depend upon the type of antimicrobial used, the number of individuals treated, the dosage regimen, and the duration of treatment. Therefore, it is vital to limit therapeutic antimicrobial use in animals and humans to those situations where they are needed.

The veterinary profession shares the concerns of the public, governmental agencies, and public health community regarding the broad issue of antimicro-

bial resistance and specifically the potential risk of resistance developing in animals with subsequent transfer to humans. Because of those concerns, to maintain the long-term effectiveness of antimicrobials for animal and human use and to increase the possibility of future antimicrobial drug approvals for the treatment of animals, the American Veterinary Medical Association and the American Association of Bovine Practitioners are committed to judicious and prudent use of antimicrobials by veterinarians for the prevention, control, and treatment of animal diseases.

The AVMA started a profession-wide initiative, including companion and food animal practitioner groups, to develop and implement judicious use principles for the therapeutic use of antimicrobials by veterinarians. The AVMA Executive Board approved a general set of judicious use principles in November 1998. Concurrent with the AVMA initiative, the AABP was addressing antimicrobial use in cattle through articles in the *Bovine Practitioner*, presentations at annual meetings, in discussions on aabp-l (an internet list server forum for AABP members) and a committee charged with developing guidelines for the use of antimicrobials in cattle. The AABP Board of Directors approved Prudent Drug Use Guidelines in March 1999. In the following pages, both the general AVMA judicious therapeutic antimicrobial use principles and the AABP guidelines for prudent use of drugs, with more specific examples, will be presented.

The overarching position of the AVMA is, “When the decision is reached to use antimicrobials for therapy, veterinarians should strive to optimize therapeutic efficacy and minimize resistance to antimicrobials to protect public and animal health.” The objectives of the AVMA are to:

- support development of a scientific knowledge base that provides the basis for judicious therapeutic antimicrobial use,
- support educational efforts that promote judicious therapeutic antimicrobial use,
- preserve therapeutic efficacy of antimicrobials, and
- ensure current and future availability of veterinary antimicrobials.

Judicious use of antimicrobials is an integral part of good veterinary practice. It is an attitude to maximize therapeutic efficacy and minimize selection of resistant microorganisms. Judicious use principles are a guide for optimal use of antimicrobials. They should not be interpreted so restrictively as to replace the professional judgment of practitioners or to compromise animal health or welfare. In all cases, animals should receive prompt and effective treatment as deemed necessary by the prescribing or supervising veterinarian.

There are fifteen general principles which emphasize preventive actions to avoid disease, suggest other options before choosing to use antimicrobials, or the use of drugs, when possible, that are less important to human and animal needs.

The principles with explanatory notes are:

1) Preventive strategies, such as appropriate husbandry and hygiene, routine health monitoring, and immunizations, should be emphasized.

Antimicrobial use should not be viewed in isolation from the disciplines of animal management, animal welfare, husbandry, hygiene, nutrition, immunology and vaccination. Diseases must be controlled to reduce the need for antimicrobial use and they can only be controlled successfully by preventive medicine. The objective is to prevent disease to the greatest extent possible so that antimicrobial treatment is not required. In food animals, antimicrobial use should always be part of, and not a replacement for, integrated disease control programs. These programs are likely to involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in stocking rates, vaccination, and other measures. These examples of preventive strategies are not exhaustive. Continued antimicrobial use in such control programs should be regularly assessed regarding effectiveness and whether such use can be reduced or stopped.

Additional research is needed on economical and efficacious alternatives to the use of antimicrobials and to evaluate their effects on selection of resistant bacteria. Evaluation is needed of vaccines, probiotics, competitive exclusion principles and products, nutrition, and new health technologies and strategies.

2) Other therapeutic options should be considered prior to antimicrobial therapy.

Cases of lameness may be due to trauma and not accompanied by infection that would require antimicrobial treatment. Calf scours may only need to be treated with fluid replacement, not with antimicrobials. Animals experiencing viral-induced disease may be supported through good nutrition and administration of drugs such as non-steroidal anti-inflammatory drugs with anti-pyretic properties.

3) Judicious use of antimicrobials, when under the direction of a veterinarian, should meet all the requirements of a valid veterinarian-client-patient relationship.

A veterinarian is required to direct the use of prescription antimicrobials or antimicrobials being used in an extralabel manner. This direction may only take place within the context of a valid veterinary-client-patient relationship (VCPR). A valid VCPR exists when **all** of the following conditions have been met:

- a) The veterinarian has assumed the responsibility for making clinical judgments regarding the health of the animal(s) and the need for medical treatment, and the client has agreed to follow the veterinarian's instructions.
- b) The veterinarian has sufficient knowledge of the animal(s) to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s) or by medically appropriate and timely visits to the premises where the animal(s) are kept.
- c) The veterinarian is readily available for follow-up evaluation, or has arranged for emergency coverage, in the event of adverse reactions or failure of the treatment regimen.

When it is not possible to make a direct clinical evaluation, the diagnosis should be based on past experience, on knowledge of the farm epidemiological status, and historical and/or on-going susceptibility testing.

4) Prescription, Veterinary Feed Directive, and extralabel use of antimicrobials

must meet all the requirements of a valid veterinarian-client-patient relationship.

Federal regulations mandate a valid VCPR for the dispensing and use of prescription and VFD drugs and for extralabel use of drugs. Extralabel use of antimicrobials in or on animal feeds is prohibited.

5) Extralabel antimicrobial therapy must be prescribed only in accordance with the Animal Medicinal Drug Use Clarification Act amendments to the Food, Drug, and Cosmetic Act and its regulations.

No drug can be marketed unless its quality, safety, and efficacy have been demonstrated. Therefore, the first line of choice should be based on the products approved for the species and the indication concerned. When no suitable product is approved for a specific condition or species, or the approved product is considered to be clinically ineffective, the choice of an alternative product should be based, whenever possible, on the results of valid scientific studies and a proven efficacy for the condition and species concerned.

- a) For food animals, extralabel drug use (ELDU) is not permitted if a drug exists that is labeled for the food animal species and contains the needed ingredient, is in the proper dosage form, is labeled for the indication, and is clinically effective.
- b) ELDU is permitted only by or under the supervision of a veterinarian.
- c) ELDU is allowed only for FDA approved animal and human drugs.
- d) ELDU is permitted for therapeutic purposes only when an animal's health is suffering or threatened. ELDU is not permitted for production drugs (e.g., growth promotion).
- e) ELDU in feed is prohibited.
- f) ELDU is permitted for preventative purposes when an animal's health is threatened.
- g) ELDU is not permitted if it results in a violative food residue, or any residue that may present a risk to public health.
- h) ELDU requires scientifically based drug withdrawal times to ensure food safety.
- i) The record and labeling requirements must be met.
- j) The FDA prohibits specific ELDU. For example, the following drugs are prohibited for extralabel use in food animals: chloramphenicol, clenbuterol, diethylstilbestrol, dimetridazole, ipronidazole, other nitroimidazoles, furazolidone (except for approved topical use), nitrofurazone (except for approved topical use), sulfonamide drugs in lactating dairy cows (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxyypyridazine), fluoroquinolones, and glycopeptides (example is vancomycin).

6) Veterinarians should work with those responsible for the care of animals to use antimicrobials judiciously regardless of the distribution system through which the antimicrobial was obtained.

Since 1988, FDA has approved new therapeutic antimicrobials for use in animals as prescription-only products. The prescription-only policy is based on the need to assure the proper use of antimicrobials through precise diagnosis and

correct treatment of disease to minimize animal suffering and to avoid drug residues in food. However, many of the older antimicrobials are available for over-the-counter sale to producers. For these drugs, the FDA has determined that the producers can use the antimicrobials, safely and effectively, as directed on the label. Regular, close veterinary involvement can assist the producers by providing informed advice and guidance on judicious use. Extralabel use of over-the-counter antimicrobials would require that a veterinarian and the producer follow the constraints of AMDUCA, including the establishment of a valid veterinary-client-patient relationship.

Quality assurance programs also provide guidance to producers and veterinarians on proper use of drugs. The Nebraska Beef Quality Assurance Program and the Wisconsin VMA AMDUCA Task Force are outstanding examples.

7) Regimens for therapeutic antimicrobial use should be optimized using current pharmacological information and principles.

For labeled use of an antimicrobial, the most accessible source of information is the label, which includes the package insert. For extralabel use, the Food Animal Residue Avoidance Databank can assist with determinations of withdrawal times. To assist with determinations of possible alternatives to antimicrobial therapy and with drug use regimens when using antimicrobials, several veterinary organizations and two producer organization are funding the development of the Veterinary Antimicrobial Decision Support System (VADS). The objective of VADS is to provide veterinarians with a source of easily accessible information on the therapy of specific diseases to help them make informed treatment decisions. The new decision support system will allow veterinarians to access current, peer-reviewed information when selecting treatment regimens. The available information will include a full-range of therapeutic options, and the supporting data for each antimicrobial available to treat a disease. The pathogen data will include susceptibility profile information, when available, as well as an interpretation of susceptibility breakpoints as related to clinical efficacy.

The choice of the right antimicrobial needs to take into account pharmacokinetic parameters, such as bioavailability, tissue distribution, apparent elimination half-life, and tissue kinetics to ensure the selected therapeutic agent reaches the site of infection. Duration of withdrawal times may be a factor in choosing suitable products. Consideration must also be given to the available pharmaceutical forms and to the route of administration. Prolonged oral use should be avoided, as most of the concerns with regard to resistance are associated with the selection and transfer of resistant, zoonotic bacteria that inhabit the gut.

8) Antimicrobials considered important in treating refractory infections in human or veterinary medicine should be used in animals only after careful review and reasonable justification. Consider using other antimicrobials for initial therapy.

In this context, this principle takes into account development of resistance or cross-resistance to important antimicrobials. In December 1998, the FDA made available "A Proposed Framework for Evaluating and Assessing the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals"

(Framework Document). A concept introduced by the Framework Document is the categorization of antimicrobials based on their unique or relative importance to human medicine and their likelihood of affecting human exposure to food-borne pathogens. While the criteria for categorization remain under discussion, it is expected that antimicrobials such as the fluoroquinolones and third generation cephalosporins will probably be classified in the most important category. The fluoroquinolones are also very important for the treatment of colibacillosis in poultry.

9) Use narrow spectrum antimicrobials whenever appropriate.

To minimize the likelihood of broad antimicrobial resistance development, where an appropriate narrow spectrum agent is available, it should be selected in preference to a broad spectrum agent.

10) Utilize culture and susceptibility results to aid in the selection of antimicrobials when clinically relevant.

Susceptibility profiles can vary between herds and flocks. Periodic culture and susceptibility testing can provide historical data on which to base future empirical treatment as well as assist in selecting a treatment for refractory infections. Ideally, the susceptibility profile of the causal organism should be determined before therapy is started. The veterinarian has a responsibility to determine the applicability of the breakpoints used by the lab for the specific disease indication being considered. In disease outbreaks involving high mortality or where there are signs of rapid spread of disease, treatment may be started on the basis of a clinical diagnosis and previous applicable susceptibility results before current samples are submitted for susceptibility evaluation or results are obtained. Even so, the susceptibility of the suspected causal organism should, where possible, be determined so that if treatment fails it can be changed in the light of the results of susceptibility testing. Antimicrobial susceptibility trends should be monitored over time, and such monitoring used to guide clinical judgement on antibiotic usage.

Susceptibility tests are intended to be a guide for the practitioner, not a guarantee, that an antimicrobial will be effective in therapy. Susceptibility testing can only give an indication of what the clinical activity of the drug will be. The projection of clinical efficacy from an in vitro MIC determination is much more accurate for antimicrobials with validated breakpoints for the specific indication. The effect of the drug in vivo depends on its ability to reach the site of infection in a high enough concentration, the nature of the pathological process, and the immune responses of the host.

11) Therapeutic antimicrobial use should be confined to appropriate clinical indications. Inappropriate uses such as for uncomplicated viral infections should be avoided.

Veterinarians should use their professional knowledge and clinical judgment to decide whether viral infections may involve or predispose to a superimposed bacterial infection.

12) Therapeutic exposure to antimicrobials should be minimized by treating only for as long as needed for the desired clinical response.

Theoretically, infections should be treated with antimicrobials only until the host's defense system is adequate to resolve the infection. While it may be difficult to judge optimal treatment duration, limiting the duration of use to only that required for therapeutic effect will minimize the exposure of the bacterial population to the antimicrobial. The adverse effects on the surviving commensal microflora are minimized and the medical impact on the remaining zoonotic organisms is reduced. However, treatment for too short a period can also be problematic because it can lead to recrudescence of the infection. It is then possible that a higher percentage of the pathogens involved in the recrudescence episode have reduced susceptibility to the antimicrobial.

13) Limit therapeutic antimicrobial treatment to ill or at risk animals, treating the fewest animals indicated.

In some classes of livestock, if a number of animals in a group have overt signs of disease, both sick and healthy animals may be treated with therapeutic levels of an antimicrobial. This is intended to cure the clinically affected animals, reduce the spread of the disease, and arrest disease development in animals not yet showing clinical signs.

It is recognized that strategic, metaphylactic medication of a specific group of animals may be appropriate in certain precisely defined circumstances. However, this should be part of an integrated disease control program and the need for such medication should be regularly re-evaluated. The use of antimicrobials in the absence of clinical disease or pathogenic infections should be restricted to situations where past experience indicates that the risk is high that a group of animals may develop disease if not treated. In addition, long-term administration to prevent disease should not be practiced without a clear medical justification.

14) Minimize environmental contamination with antimicrobials whenever possible.

Unused antimicrobials should be properly disposed. Also some antimicrobials may be environmentally stable in manure. If the antimicrobials are not bound in an inactive form, environmental exposure could contribute to resistance development. Consideration may need to be given to disposal methods that will not recycle resistant organisms to humans or animals.

15) Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.

Outcome records can greatly assist with design of future empiric treatment regimens.

The implementation of these general judicious use principles, and the more specific examples in the prudent antimicrobial use guidelines given in the following sections, will reduce the development of resistant zoonotic pathogens and commensals in animals and will lessen the risk of a human health impact related to the therapeutic use of antimicrobials in animals.

Application of Judicious and Prudent Microbial Use Principles by Dairy Cattle Practitioners

Veterinarians treating cattle with antimicrobials have always had three responsibilities: first, to diagnose, prevent and, when necessary, treat disease in their patients; second, to optimize the production and health maintenance resources of those who own and care for their patients; and third, to meet the expectations regarding the safety of food animal production of those who choose to consume food products derived from their clients' cattle. Consumers should expect that veterinarians have prudently and judiciously used antimicrobials in order to minimize the emergence or development of antimicrobial resistance.

There has never been a time when veterinarians did not have all three responsibilities. In the past, some veterinarians may have chosen treatment options based on perceived success in treating an individual patient or patients on an individual farm, as being the only important responsibility. To diminish the importance of the other two responsibilities is poor medical and business decision management.

Conservation of available antimicrobials requires that veterinarians select and use them appropriately. If veterinarians do not, the FDA Center for Veterinary Medicine will have to respond as the laws and regulations require. The result will be an impression by consumers of food animal products and by groups advocating positions of food safety that cattle-derived food products are not produced with sound practices. While the magnitude of the impact of antimicrobial use in cattle on the development of antibiotic resistance for human pathogens may continue to be discussed, the importance of prudent and judicious antimicrobial use has never been greater.

It is false economic benefit to choose an inappropriate antimicrobial regimen if it undermines the veterinary profession's credibility with consumers or those who implement our national food animal drug laws and regulations. When antimicrobial choices are diminished, veterinarians' ability to enhance productivity and to treat disease will also be diminished. The focus of both veterinarians and producers should be on the safety and needs of the consumer.

The production of safe and wholesome animal products for human consumption should be a primary goal of veterinarians caring for dairy cattle. In reaching that goal, as mentioned in the general principles, emphasis should be placed on practitioners being committed to preventive immune system management through the use of vaccines, parasiticides, stress reduction, and proper nutritional management. Proper and timely management practices can reduce the incidence of disease and therefore reduce the need for antimicrobials. Nevertheless, antimicrobials will remain a necessary tool to manage infectious diseases in dairy herds.

To reemphasize the points made earlier, prudent and judicious use of antimicrobials is necessary to reduce animal pain and suffering, to protect the

economic livelihood of dairy producers, to ensure the continued production of foods of animal origin, and to minimize the shedding of zoonotic bacteria into the environment and potentially the food chain. The following are specific recommendations for the prudent and judicious use of antimicrobials in dairy cattle and are provided for each of the prudent antimicrobial use guidelines adopted by the AABP.

The veterinarian should accept responsibility for helping clients design management, immunization, housing, and nutritional programs that will reduce the incidence of disease and the need for antimicrobials. Providing adequately ventilated housing, such as with calf hutches, minimizes the potential for the development of bovine respiratory disease. Colostrum management programs and their monitoring will enhance the health of the young replacement heifer.

Adequate selenium and vitamin E nutrition will enhance udder health and aid in mastitis prevention as well as minimizing the incidence of retained placenta in the postpartum cow. Ensuring adequate pre-calving nutrition of the cow, particularly protein, is of paramount importance. This will enhance the passive transfer of antibodies from high quality colostrum to the neonatal calf, and has been proven to provide health benefits throughout the life of the animal. When a poorly functioning immune system results in an increased level of respiratory disease, efforts to identify and correct immunosuppressive factors should be implemented. The reduction in morbidity and mortality, and the related decrease in the need for antimicrobials, may be dramatic where levels of nutrients such as copper, zinc and selenium are optimized.

The use of antimicrobials only within the confines of a valid veterinarian-client-patient relationship (see page 5), for both dispensing and the issuance of prescriptions, has been recommended by the American Association of Bovine Practitioners. In addition, extralabel usage should be within the provisions contained within the AMDUCA regulations (see page 6). All veterinarians should carefully review their willingness to respond to producers' requests for antimicrobial use recommendations. If a veterinarian is not the person responsible for diagnosis of disease conditions on a dairy cattle operation, is not available for questions or concerns following treatment with antimicrobials or has not accepted the responsibility for health care of the cattle on that operation, they will not be in position to optimize antimicrobial use or to minimize the development of resistance to antimicrobials. Veterinarians prescribing, dispensing, or administering antimicrobials to cattle should utilize the services of FARAD or other unbiased and reputable sources to provide scientifically sound withdrawal times for producers.

Veterinarians should properly select and use antimicrobial drugs. Veterinarians should participate in continuing education programs that include therapeutics and emergence and/or development of antimicrobial resistance. Human food safety concerns are discussed at numerous regional, state and national meetings every year. At least some portion of required Continuing Education hours should be received on the topic of antimicrobial susceptibility

of animal and potential zoonotic pathogens. Material accessible from reliable sources such as the FDA/CVM, FARAD, and AABP home pages and from the list of additional sources of information given at the end of this paper should be incorporated into treatment considerations and recommendations.

A dairy cattle veterinarian should have strong clinical evidence of the identity of the pathogen causing the disease, based upon clinical signs, history, necropsy examination, laboratory data and past experience before making a recommendation for antimicrobial use. In addition, they should periodically monitor herd pathogen susceptibility and therapeutic response to detect changes in microbial susceptibility and to re-evaluate antimicrobial selections. Records and observations on individual operations or within groups of cattle within a veterinarian's area of practice may be very helpful in making and modifying antimicrobial recommendations. Historical diagnostic material obtained from post mortem examinations, trans-tracheal washes and milk cultures may be utilized to allow the application of narrow spectrum antimicrobials when necessary and only when necessary. Although the susceptibility profiles of pathogens may be skewed in diagnostic data reports (due to prior therapy of some of the animals), these reports are still a useful barometer of changes in the populations of pathogens encountered by food animal veterinarians.

The animal's origin prior to their arrival should be considered when establishing a diagnosis in herd outbreaks and when developing treatment protocols, including therapeutic or metaphylactic antimicrobial use. Implementation of applicable and proven biosecurity measures for purchased animals may reduce the need for antimicrobial therapy.

Antimicrobials should be used at a dosage and duration appropriate for the condition treated. The goals of therapy should be to alleviate clinical signs and minimize recurrence of clinical disease. Treatment of subclinical mastitis caused by *Streptococcus agalactiae* should be directed by antimicrobial susceptibility information and should be administered so as to provide 24 hours of therapeutic levels which will result in elimination of the bacteria in 95% of treated cases. In the absence of data showing otherwise, practitioners should strive for the shortest duration of therapy that results in satisfactory clinical response.

Product choices and regimens should be based on available laboratory and label (including package insert) information, additional data in the literature and consideration of the pharmacokinetics, spectrum, and pharmacodynamics of the drug. With this information, combined with the clinical and laboratory information previously mentioned, prudent and judicious antimicrobial use decisions are possible. The label, dose, route, frequency, and duration should be followed whenever possible.

Antimicrobials should be used with specific clinical outcome(s) in mind, such as fever reduction, return of mastitic milk to normal, to eliminate or reduce shedding, contagion, and recurrence of disease. The use of appropriately selected intramammary antimicrobials in cases of mastitis caused by Gram positive bacteria will reduce the time to return to normal mammary secretion.

The same does not hold true for Gram negative organisms. Specific outcome criteria aid in preventing exceptionally long therapy and indicating when the current therapy is unsatisfactory.

Periodically monitor herd pathogen susceptibility and therapeutic response, especially for routine therapy such as dry cow intramammary antibiotics, to detect changes in microbial susceptibility and to evaluate antimicrobial selections. Susceptibility patterns for mastitis pathogens should be evaluated periodically to determine the appropriate class of antimicrobials to administer.

Use products that have the narrowest spectrum of activity and known efficacy in vivo against the pathogen causing the disease problem. In clinical situations, the boundary between narrow and broad spectrum of activity may be difficult to determine. Narrow and broad spectrum levels of activity will vary depending upon both the bacteria affected and the regimen chosen. In spite of the difficulty in confining antimicrobial use to a narrow spectrum of activity, resistance to antimicrobials should be minimized by selecting an antimicrobial with a narrow spectrum of activity whenever possible.

Utilizing antimicrobials such as procaine penicillin G for cases of infection with anaerobic bacteria, such as exist in infectious pododermatitis and toxic uterine infections, could be prudent at labeled or some extralabel dosage, penicillin would be considered a narrow spectrum antimicrobial (see glossary). However, even in the most ideal situation, the possibility of antimicrobial use affecting more than just the target pathogen exists.

Antimicrobials should be used at a dosage appropriate for the condition treated and for as short a period of time as reasonable. Therapy should be discontinued when it is apparent that the immune system can manage the disease, reduce pathogen shedding and minimize recurrence of clinical disease or development of the carrier state. The National Mastitis Council recommends that intramammary antimicrobial therapy should provide for 72 hours of levels at or above the MIC of the pathogen causing a clinical mastitis to provide for the greatest chance of microbiological cure in the affected quarter. The veterinarian should rely on records and valid published information to justify their clinical judgement on the proper time to discontinue therapy.

When possible, antimicrobials of lesser importance in human medicine should be chosen before choosing a newer generation animal antimicrobial that may be in the same class as a human antimicrobial that may be used as the primary or sole treatment for a human infection. An antimicrobial for which emergence of resistance is expected to be in an advanced stage, should also not be chosen. Products such as fluoroquinolones should be reserved for cases that can be predicted to be refractory to other therapies and should be used according to label directions or AMDUCA regulations. No extralabel use of fluoroquinolones is provided for in the AMDUCA regulations and this use is banned by law. Therefore, fluoroquinolones cannot be used in animals intended for dairy purposes.

Antimicrobials labeled for use for treating the condition diagnosed should be used whenever possible. The label, dose, route, frequency, and duration should be followed whenever possible. Antimicrobial therapy of clinical mastitis, when indicated, as with the Gram positive organisms, should provide adequate duration of therapy.

Combination antimicrobial therapy should be discouraged unless there is information to show increase in efficacy or suppression of resistance development for the target organism. Compounding of antimicrobial formulations should be avoided. There is little scientific information which supports the theories that either combinations of antimicrobials or compounded antimicrobials are more effective than the use of a solitary antimicrobial labeled for use in infections encountered in cattle. We do know that combinations of antimicrobials broaden the exposure of pathogens and commensal bacteria in the animal.

When appropriate, local therapy (e.g. intramammary, intrauterine, topical) is preferred over systemic therapy. Labeled choices for local therapy may be very limited, but extralabel use would be appropriate if the requirements for extralabel use described on pages 5 and 6 were followed. For example, an extralabel use of a intrauterine antibacterial labeled for use in another animal species would be appropriate in cattle if no labeled antibacterial provided the efficacy or duration of action needed. An external wound dressing without a cattle label would be appropriate if efficacious and if, as in all cases of extralabel use, residues and contamination were prevented by the choice of withdrawal period.

Treatment of chronic cases or those with a poor chance of recovery should be avoided. Chronic, non-responsive cases should be removed or isolated from the remainder of the herd and use of antimicrobials halted.

Prophylactic or metaphylactic use of antimicrobials should be based on a group, source or production unit evaluation rather than being utilized as standard practice. The metaphylactic use of lower than label doses of antimicrobials to reduce expense should be actively discouraged.

Veterinarians should endeavor to ensure proper on-farm drug use. Drug integrity should be protected through proper handling, storage and observation of the expiration date. Due to the potential for inspections of drug storage facilities, the attending veterinarian should seek to perform periodic inspections of the premises.

Prescription or dispensed drug quantities should be appropriate to the production-unit size and expected need so that stockpiling of antimicrobials on the farm is avoided. The amount of a particular pharmaceutical allowed for prescription from a drug distributor should be consistent with previous and expected disease incidence and treatment requirements. If the antimicrobials are not dispensed by the veterinarian, adequate lines of communication between the veterinarian, animal producer, and pharmaceutical distributor, coupled with

appropriately scripted and labeled products, enhance proper drug usage. The prescribing veterinarian should seek to review or receive copies of invoices of scripted drug purchases to insure that appropriate quantities are being purchased for use.

The veterinarian should train farm personnel who use antimicrobials on indications, dosages, withdrawal times, route of administration, injection site precautions, storage, handling, record keeping, and accurate diagnosis of common diseases. The veterinarian should ensure that labels are adequate to instruct farm personnel on the correct use of antimicrobials. The veterinarian should be able to provide frequent inspections of inventory and treatment records.

Veterinarians are encouraged to provide written, updated protocols for diagnosis and treatment to clients whenever possible. Those protocols should describe conditions and provide instructions for antimicrobial use at a farm or unit when a veterinarian is unavailable.

Additional Sources of Information Regarding Antimicrobial Use

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Beef Sessions on Antibiotic Resistance, in *Proceedings of 32nd Annual Convention of American Association of Bovine Practitioners*, September 1999, pages 71-122.

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Helpful Tips for Extra-Label Drug Use, in *Journal of American Veterinary Medical Association*, vol 212, #5, March 1, 1998; #7, April 1, 1998; #9, May 1, 1998; #11, June 1, 1998.

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GLOSSARY

Antibiotic—a chemical substance produced by a microorganism which has the capacity, in dilute solutions, to inhibit the growth of or to kill other microorganisms.

Antimicrobial—an agent that kills bacteria or suppresses their multiplication or growth. This includes antibiotics and synthetic agents. This excludes ionophores and arsenicals.

Narrow Spectrum Antimicrobial—an antimicrobial effective against a limited number of bacterial genera often applied to an antimicrobial active against either Gram-positive or Gram-negative bacteria.

Broad Spectrum Antimicrobial—an antimicrobial effective against a large number of bacterial genera; generally describes antibiotics effective against both Gram-positive and Gram-negative bacteria.

Antibiotic Resistance—a property of bacteria that confers the capacity to inactivate or exclude antibiotics or a mechanism that blocks the inhibitory or killing effects of antibiotics.

Extralabel—Extralabel use means actual use or intended use of a drug in an

animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.

Immunization—the process of rendering a subject immune or of becoming immune, either by conventional vaccination or exposure.

Monitoring—monitoring includes periodic health surveillance of the population or individual animal examination.

Therapeutic—treatment, control, and prevention of bacterial disease

Veterinarian-Client-Patient Relationship (VCPR)—A VCPR exists when all of the following conditions have been met:

1. The veterinarian has assumed the responsibility for making clinical judgments regarding the health of the animal(s) and the need for medical treatment, and the client has agreed to follow the veterinarian's instructions.
2. The veterinarian has sufficient knowledge of the animal(s) to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s) or by medically appropriate and timely visits to the premises where the animal(s) are kept.
3. The veterinarian is readily available for follow-up evaluation, or has arranged for emergency coverage, in the event of adverse reactions or failure of the treatment regimen.

Veterinary Feed Directive (VFD) Drug—The VFD category of medicated feeds was created by the Animal Drug Availability Act of 1996 to provide an alternative to prescription status for certain therapeutic animal pharmaceuticals for use in feed. Any animal feed bearing or containing a VFD drug shall be fed to animals only by or upon a lawful VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice.



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