

Judicious Use
of Antimicrobials for

Aquatic Veterinarians





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EDUCATIONAL MATERIAL FOR VETERINARIANS ABOUT JUDICIOUS USE OF ANTIMICROBIALS IN AQUATIC ANIMALS

Introduction

Antimicrobials, including antibiotics, are needed for the relief of pain and suffering associated with diseases in animals, including fish and other aquatic animals that are caused by bacteria, rickettsials, and other microorganisms such as protozoa (coccidia). For food animals, including farmed aquatic animals, the gains that have been made in food production capacity would not have been possible without the ability to prescribe safe and effective drugs to contain the threat of disease in these animals. The increased capacity of the United States to produce aquatic animals for consumption has kept an important source of 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."¹ 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."² However, the use of antimicrobials in aquatic food animals is not without risk.

This document has therefore been prepared to help veterinarians treating aquatic animals with their efforts to use antimicrobials judiciously to maintain the effectiveness of these drugs in the treatment and prevention of bacterial diseases of aquatic animals grown for food production, while minimizing the development of resistance in human and animal pathogens.

Antimicrobial Resistance Concerns

In recent years, concerns about the use of antimicrobial products in food-producing animals have focused on human food safety. Foods of animal origin are sometimes identified as the vehicles of food-borne disease in humans, including resistant food-borne pathogens, and of genetic material that confers resistance. Other concerns have been raised regarding the possible risk of antimicrobial resistance development in bacteria within the environment, and the potential for the occurrence and/or maintenance of zoonotic pathogens (i.e., *Mycobacterium*, *Streptococcus*) in an aquatic population.

Much of the information on antimicrobial resistance is derived from studies on the effect of antimicrobial agents on terrestrial animal and human pathogens and commensal organisms. But aquatic animals and microorganisms live in very different environments compared to terrestrial species. Unfortunately, information on antimicrobial resistance of aquatic microorganisms is frequently lacking and is poorly understood. Irrespective, it is prudent for veterinarians to be aware of the possibilities and utilize antimicrobials judiciously in concert with other disease prevention and control practices.

Natural mechanisms of resistance to antimicrobials probably existed even before such therapeutants were first used by humans. However, this intrinsic form of resistance is not a major source of concern for human and animal health. Physicians and veterinarians select antimicrobials for treatment based on the labeled spectrum of activity that has been determined during the drug development process. Drug-resistant organisms of more recent concern have instead mainly 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 antimicrobials. The presence of the drug serves as a selecting mechanism to suppress susceptible microorganisms and promote the growth of resistant mutants. Spontaneous mutations are vertically transmissible from parent to progeny. Resistance can also develop as a result of transfer of genetic material between bacteria. Plasmids, which are small extra-chromosomal DNA molecules, and 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, in some cases, more than one mechanism may operate simultaneously or sequentially in microorganisms for the same antimicrobial. Microorganisms resistant to a certain antimicrobial may also be resistant to other antimicrobials that share the same mechanism of action in, or attachment to, the microorganism. 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-streptogramins). 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 under some circumstances also select for resistance to the other antimicrobials.

Definitive answers about the safety of antimicrobial use in animals remain scientifically challenging, but 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 used are killed (by bactericides) or put at a competitive disadvantage through reduction of numbers (by bacteriostats), 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.¹

JUDICIOUS USE

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.

The veterinary profession shares the concerns of the public, governmental agencies, and public health community regarding the broad issue of antimicrobial resistance and specifically the potential risk of resistance developing in animals with subsequent transfer to humans. 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. 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 is 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, which were updated and re-approved in 2004. In the following pages, both the general AVMA judicious therapeutic antimicrobial use principles and the guidelines for prudent use of drugs, with more specific examples relating to aquatic animal models, will be presented.

The overarching AVMA position regarding antimicrobial use 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 this policy 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.

There are fifteen general principles found in the AVMA’s policy guidelines for antimicrobial use that emphasize preventive actions to avoid disease and provide options before choosing to use antimicrobials, or other drugs that are of relevance to animal and human 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. The optimal control or elimination of bacterial disease, which will reduce the need for antimicrobial use, is most successfully achieved through preventative protocols. In food animals, antimicrobial use should always be part of, and not a

replacement for, integrated disease control programs, which may involve hygiene and disinfection procedures, biosecurity measures, management alterations, changes in density, vaccination, and fallowing, among other measures. Any and all 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 for different types 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.

Water quality testing along with timely environmental and animal management procedures can reduce or eliminate physiologically stressful conditions that may predispose aquatic animal populations to infection and subsequent disease development. Other examples include parasite control programs (integrated pest management) and the appropriate use of vaccines and bacterins, which may further reduce the occurrence of disease.

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

Veterinary oversight is required for the use of certain FDA-approved antimicrobials, or antimicrobials used in an extralabel manner. This direction may only take place within the context of a veterinarian-client-patient relationship (VCPR). As stipulated in the Code of Federal Regulations (21 CFR Part 530) a VCPR exists when *all* of the following conditions have been met:

- a) A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian.
- b) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s).

c) The practicing veterinarian is readily available for followup in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept.

When it is not possible to make a direct clinical evaluation of all affected animals, the diagnosis or need for antimicrobial use should be based on past experience, on knowledge of the facility's epidemiological status, and historical and /or ongoing susceptibility testing.

4) Prescription, Veterinary Feed Directive, and extralabel use of antimicrobials must meet all the requirements of a veterinarian-client-patient relationship.

Federal regulations mandate a 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; however, the FDA-CVM has published a Compliance Policy Guide that sets out specific conditions under which the agency will not take enforcement action regarding the extralabel use of certain medicated feeds in aquatic animal species.³

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

No drug can be marketed unless its quality, safety, and effectiveness have been demonstrated. The first choice must be the product approved for the species, the disease in question, and the dosage indicated on the label. When no suitable product is approved for a specific disease condition or animal species, or the approved product is considered to be clinically ineffective at the labeled dosage, extralabel drug use (ELDU) is permissible. The choice of an alternative product or therapeutic regimen should be based, whenever possible, on the results of valid scientific information demonstrating effectiveness for the condition and safety for the species concerned. Extralabel drug use has several constraints or conditions including:

a) For food animals, 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 is only permitted for preventative purposes when an animal's life or health is threatened.
- f) ELDU is not permitted if it results in a violative food residue, or any residue that may present a risk to public health.
- g) ELDU requires scientifically based drug withdrawal times to ensure food safety.
- h) ELDU medical records, including advice to clients, and labeling requirements must be met.
- i) The FDA specifically prohibits extralabel use of certain drugs and families of drugs in food animals, including aquatic animals used as food: chloramphenicol, clenbuterol, diethylstilbestrol, dimetridazole, ipronidazole, other nitroimidazoles, furazolidone, nitrofurazone, sulfonamide drugs (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine), fluoroquinolones, glycopeptides (example is vancomycin), and phenylbutazone.
- j) Normally ELDU in feed is not permitted. However in the case of minor species, including aquatic animals, FDA's Compliance Policy Guide (CPG), section 615.115, entitled "Extralabel Use of Medicated Feeds for Minor Species" provides guidance to veterinarians concerning the Agency's exercise of regulatory discretion with regard to the extralabel use of medicated feeds for minor species. While extralabel use is generally prohibited in feed, the FDA recognizes that feed is the only practicable methods of medicating fish. Therefore, if veterinarians stay within the guidance, they should not expect disciplinary action by FDA.

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, two antimicrobials (i.e., oxytetracycline and sulfadimethoxime/ormetoprim) are available for over-the-counter sale to producers for treatment of certain species of aquatic animals meeting specific conditions of infection and/or disease. 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 producers by providing informed advice and guidance on judicious use. Extralabel use of over-the-counter antimicrobials requires that veterinarians and producers follow the conditions set out in the Compliance Policy Guide described in item 4 and 5 above if the means of administration is through feed.

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 (FARAD) can assist with determinations of withdrawal times.

The choice of an optimal 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 at the required concentration and for the required time period. A database of pharmacokinetic data in fish has been recently compiled and a link will be available through FDA/CVM's home page.⁴ Duration of withdrawal times may be a factor in choosing suitable products. Consideration must also be given to the available and approved pharmaceutical forms and to the route of administration.

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 some important antimicrobials used in human medicine. A concept introduced by FDA/CVM Guidance for Industry #152, titled "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern", 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. Antimicrobials such as the fluoroquinolones and third generation cephalosporins are classified in the 'critically important' category.

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.

Antimicrobial susceptibility or sensitivity profiles can vary among aquatic animal populations, e.g. different production sites and different groups within sites. Periodic culture and susceptibility testing can provide historical data on which to base future empirical treatment as well as to assist in selecting a treatment for refractory infections. Ideally, the susceptibility profile of the causal organism should be determined before therapy is started. Standardized methods for testing aquatic bacteria have recently been developed and are available from the Clinical and Laboratory Standards Institute (formerly NCCLS, <http://www.nccls.org/>).^{5,6} The veterinarian has a responsibility to determine the applicability of the antimicrobial susceptibility breakpoints (i.e., drug concentrations) used by the laboratory for the specific drug and pathogen 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 laboratory results are obtained. Irrespective of treatment, the susceptibility of the suspected causal pathogen should, where possible, be determined so that if the treatment regimen is ineffective it can subsequently be changed in the light of the results of susceptibility testing. Antimicrobial susceptibility trends should be monitored over

time, and such monitoring should be used to guide clinical judgement on future antibiotic usage.

Susceptibility tests, which are *in vitro* assays, are intended to be a guide for the practitioner; they are not a guarantee that a specific antimicrobial will be effective in therapy. Susceptibility testing only provides an indication of what the possible clinical (*in vivo*) effect of the drug will be. Estimating the clinical efficacy from an *in vitro* minimal inhibitory concentration (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 for the necessary length of time, the nature of the pathological process, and the immune status and response 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 when antimicrobial treatment is indicated because of incipient secondary bacterial complication of a disease caused by other agents.

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 against pathogens will minimize the exposure of and potential adverse effects on the beneficial commensal microbial population to the antimicrobial. 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 may have reduced susceptibility to the antimicrobial.

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

In treating aquatic animals, when a number of animals in the population 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 medication of a specific group of animals may be appropriate when individuals within the group have been diagnosed with specific infectious disease. 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 there is clear epidemiological evidence for an impending disease outbreak if not treated. In addition, long-term administration of antimicrobials to prevent disease should not be practiced without a clear medical justification.

14) Minimize environmental contamination with antimicrobials.

Unused antimicrobials should be properly disposed of, possibly by returning them to pharmaceutical distributors. Although certain antimicrobial drugs will have a very limited environmental impact because the drug is bound in an inactive form or is quickly diluted or degraded, veterinarians should work with producers to ensure that aquatic animal production facilities are in compliance with relevant environmental permits that may be necessary for effluent discharge during treatment periods.

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

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

APPLICATION OF JUDICIOUS AND PRUDENT ANTIMICROBIAL DRUG USE PRINCIPLES FOR FOOD FISH VETERINARIANS

The implementation of these general judicious use principles, and the more specific examples that apply to prudent antimicrobial use in aquatic animals in the following sections, will reduce the development of resistant animal and 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. The following guidelines were written by the Aquatic Veterinary Medicine Committee and approved by the AVMA Executive Board in November 2002 to primarily apply to finfish used for food. However, they are applicable to the treatment of all aquatic animals, including molluscs and crustacean that are grown for seafood and, to a large extent; these guidelines also apply

to non-food aquatic animals that are used for display in homes or public aquaria.

INTRODUCTION

Compliance with the principles in this document will provide assurance to food fish consumers and groups advocating food safety that farm-grown fish products are produced using sound practices. The potential impact of antimicrobial drug use on pathogen susceptibility to these drugs will continue to be discussed. However, veterinarians can minimize these concerns through prudent and judicious antimicrobial use.

Veterinarians treating food fish with antimicrobial drugs have four primary responsibilities:

- To optimize stock production for those who own and care for food fish through effective disease prevention;
- To diagnose and then treat or control disease in their patients through the safe and effective use of therapeutants;
- To ensure that fish harvested for food meet established safety standards; and,
- To ensure that antimicrobial drug administration does not adversely impact the environment receiving production facility effluent

Consumers expect that veterinarians have prudently and judiciously used all therapeutants, particularly antimicrobial drugs. There is particular concern that veterinarians manage antimicrobial drug use to minimize the emergence or development of antimicrobial resistance.

Veterinarians in food fish practice are acutely aware of these responsibilities to producers and consumers. Currently there are very few antimicrobial drugs approved for use in food fish. The effective application of available antimicrobial drugs requires that veterinarians select and use these products appropriately.

Because of the limited number (and restrictions on use) of those antimicrobials available for use in aquatic animals, disease management should be based on sound biosecurity, nutrition, disease surveillance, and production management programs. Production of safe and wholesome aquaculture products for human consumption is a primary goal of veterinarians and other fish health specialists caring for food fish. To reach that goal, practitioners should emphasize disease prevention, particularly through promotion of a healthy fish immune system through vaccination, stress reduction, and careful nutritional management.⁷

Proper and timely management practices reduce the incidence of disease and therefore reduce the need for antimicrobial treatment. Despite appropriate management measures, antimicrobial drugs will remain a necessary tool to manage infectious diseases in aquaculture.

To reemphasize the points made earlier, prudent and judicious use of antimicrobial drugs is necessary to:

- Restore fish population health;
- Protect the economic livelihood of food fish producers;
- Ensure the continued production of foods of animal origin; and,
- Minimize the shedding of zoonotic bacteria into the environment and potentially the food chain.

JUDICIOUS ANTIMICROBIAL USE PRINCIPLES

The food fish veterinarian should:

Accept responsibility for helping clients design management, immunization, production unit and nutritional programs that will reduce the incidence of disease, and the need for antimicrobial treatment.

Development and implementation of appropriate disease prophylaxis through effective vaccination is likely to reduce the incidence of disease and subsequent need for antimicrobial treatment. Insuring high quality nutrition for both broodstock and rapidly growing production fish is of paramount importance and will provide health benefits throughout the production cycle. When there is an increased disease incidence, efforts to identify and correct immunosuppressive factors should be implemented. Optimal nutrition can lead to a reduction in morbidity and mortality with a consequent decrease in the need for antimicrobial treatment. Water source quality should be evaluated for use in fish production operations, including an assessment of the potential disease transmission risk from feral populations and the related need for biosecurity measures to protect production populations. This will help to prevent the introduction of additional pathogenic microorganisms that could cause diseases requiring antimicrobial treatment. Veterinarians should work closely with other fish health experts employed at the facility in the design and implementation of fish health management programs.

Use antimicrobial drugs only within the confines of a valid veterinarian-client-patient relationship, including both the dispensing and issuing of prescriptions and veterinary feed directives. Extralabel usage should be consistent with regulatory agency laws, regulations and policies.

The veterinarian must:

- Be either the person responsible for diagnosis of disease conditions on a fish production operation or working directly with a fish health professional on the production operation;
- Be available for questions or concerns following treatment with antimicrobial drugs; and,
- Accept responsibility for health care of the fish on that operation.

Under these circumstances, the veterinarian will be able to make a recommendation on appropriate antimicrobial drug treatment and minimize the development of antimicrobial resistance. Veterinarians prescribing, dispensing, or administering antimicrobials to fish should utilize the services of unbiased and reputable sources (e.g. Food Animal Residue Avoidance Databank) to provide scientifically sound withdrawal times for producers.

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, AVMA home pages, and from the many available additional sources of professional information, should be incorporated into treatment considerations and recommendations. Many aspects of fish health management, including nutrition and immunology, are topics of active research. Veterinarians should stay current in their knowledge of this research in order to develop effective disease control programs.

Have strong clinical evidence of the identity of the disease etiology, based upon history, clinical signs, necropsy, laboratory data, and/or past experience before recommending antimicrobial drug treatment.

Records and observations on individual operations or within population subgroups, such as ponds, tanks, pens, and raceways within a veterinarian's area of practice may be very helpful in developing antimicrobial drug treatment recommendations. Historical diagnostic material obtained from post mortem and moribund fish examinations may also be helpful. Diagnostic data reports are a useful barometer of changes in pathogen sensitivity patterns, although susceptibility profiles may be skewed (perhaps due to prior therapy). The status of the originating hatchery should be considered when establishing a diagnosis in disease outbreaks and when selecting a treatment protocol. Proven biosecurity measures should be implemented when fish are introduced to a production facility to reduce the need for antimicrobial therapy.

Treat food fish with antimicrobial drugs according to the product label recommendations (including indication, dosage, duration, fish species and environmental conditions).

The product label recommendations are established through sound scientific data. Veterinarians should follow these recommendations. Furthermore, the goal of therapy should be to reduce fish mortality and minimize disease recurrence. Veterinarians should strive for the lowest dosage and appropriate duration of treatment that achieves these goals. Veterinarians should rely on previous medical records and valid published information to support clinical judgments on the proper time to discontinue therapy.

The antimicrobial drug label may require specific waste handling, or may limit the concentration allowed in production facility effluent. The veterinarian should assure that the drug containing waste or effluent is handled according to the product label directions. The veterinarian should also assure that the production facility complies with appropriate federal and state laws and regulations (e.g. National Pollutant Discharge Elimination System permits) applicable to drug use and discharge before authorizing drug administration.

Choose an antimicrobial drug and treatment regimen based on available laboratory and label (including package insert) information, additional data in the literature, and consideration of the pharmacokinetics, spectrum of activity, and pharmacodynamics of the drug.

When this information is 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 except where extralabel use is necessary and falls within government laws, regulations and policies. Familiarity with extralabel use requirements is essential given the limited availability of approved antimicrobial drugs for food fish use.

Use antimicrobial drugs with a specific clinical outcome(s) in mind, including a specific target for population morbidity and/or mortality rate reduction.

Specific outcome criteria prevent unnecessarily long therapy and indicate when the current therapy is no longer effective.

Determine production population pathogen susceptibility at the first indication of increasing morbidity or mortality and monitor the therapeutic response to detect changes in microbial susceptibility and to evaluate antimicrobial selections.⁸

Routine necropsy examination of fish populations should be periodically performed, including antimicrobial susceptibility testing, to update historical information for developing treatment and control protocols.

Use products that have the narrowest spectrum of activity and known effectiveness *in vivo* against the pathogen causing the disease problem.

In clinical situations, the boundary between a 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 by the antimicrobial and the treatment 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. The food fish veterinarian presently has access to a very limited armamentarium of long-approved antimicrobial drugs. However, this situation may change as new products are developed and approved. The veterinarian needs to be attuned to the potential for change.

Choose antimicrobial drugs of lesser importance in human medicine, if these receive future food fish use approval, and do not choose an antimicrobial for which emergence of resistance is expected to be in an advanced stage.

Drugs that are of lesser importance in human medicine should be chosen before considering extralabel use of a newer generation animal antimicrobial drug (should this be permitted under future regulations). This is of particular concern if the extralabel drug is in the same class as a human antimicrobial drug that may be the primary or sole treatment for a human infection.

New antimicrobials should be reserved for cases that can be predicted to be refractory to other therapies and should be used according to label directions or extralabel drug use regulations.

Use, whenever possible, an antimicrobial drug labeled to treat the condition diagnosed.

The veterinarian should work with producers to ensure that appropriate diagnostic procedures are in place to evaluate disease causation and initiate appropriate antimicrobial therapy when indicated.⁸

Do not use combination antimicrobial drug therapy unless there is information to show that this decreases or suppresses target organism resistance development.

There are no scientific data currently available to indicate that combination antibacterial therapy is beneficial with the few products labeled for use in food fish.

Do not compound antimicrobial drug formulations.

Do not use antimicrobial drugs to treat cases with a poor chance of recovery.

Chronic, non-responsive cases, such as fish that fail to grow and/or fish that exhibit early maturation, should be removed or isolated from the population. This will reduce interfish aggression and remove individuals who are more susceptible to disease.

Do not use antimicrobial drugs prophylactically.

No antimicrobial drugs are approved for disease prevention in food fish. Veterinarians should actively discourage any consideration of this action.

Ensure proper on-farm drug use and protect antimicrobial drug integrity through proper handling, storage, and observation of the expiration date.

Prescribe, dispense or write a Veterinary Feed Directive for drug quantities appropriate to the production-unit size and expected need using the approved formulation.

The amount of a particular antimicrobial drug prescribed or written in a veterinary feed directive should be consistent with previous and expected disease incidence and treatment requirements. If the antimicrobial drug is not dispensed by the veterinarian, then good communication between the veterinarian, animal producer, feed mill and/or pharmaceutical distributor is essential. This communication

needs to be coupled with the appropriate prescription or veterinary feed directive and correct medicated feed labeling to ensure proper drug usage. At a future date when prescription or veterinary feed directive aquaculture antimicrobial drugs are approved, then the prescribing veterinarian should seek to review or receive copies of invoices of scripted drug purchases to ensure that appropriate quantities are being purchased for use.

Work with producers and/or facility fish health management personnel to ensure that farm personnel receive adequate training on the use of antimicrobial drugs including indications, diagnosis, dosages, withdrawal times, route of administration, storage, handling, and accurate record keeping.

The veterinarian should ensure that labels are adequate to instruct facility personnel on the correct use of antimicrobial drugs.

Work closely with all other fish health experts involved in fish population health management at the fish production facility.

Veterinarians are encouraged to work with producers to develop written standard operating procedures for initiating disease diagnostic activities and implementing treatment. Those protocols should include specific instructions for procedures to follow when administering antimicrobials at fish production facilities.

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Glossary:

Antibiotic - a chemical substance produced by a microorganism or chemically synthesized, 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 category includes antibiotics and synthetic agents, and excludes ionophores and arsenicals.

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

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

Antimicrobial Resistance - a property of bacteria that confers the capacity to inactivate or reduce the effectiveness of antimicrobials, or a mechanism that blocks the inhibitory or killing effects of antibiotics.

Biosecurity - reduction of risks associated with loss of production stocks; in this context biosecurity refers to preventing the introduction of new pathogenic organisms to an operation or facility, as well as, controlling pathogens already present in the operation or facility.

Extralabel Use - actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling and 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.

Fallowing - the process by which aquatic animal premises are kept vacant for a period of time; often this is associated with the control and/or management of aquatic animal pathogens.

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 agent - qualities associated with the effective treatment, control, and/or prevention of disease that includes antimicrobials, biologics, hormones, chemicals, solutions, compounds, and other agents, often collectively referred to as drugs.

Vaccination - the introduction of vaccine into the body for the purpose of inducing immunity.

Vaccine - a preparation that contains an infectious agent or its components (e.g., subunit or DNA) which is administered to stimulate an immune response that will protect an individual from illness due to that agent. Classically, a suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae) administered for the prevention, amelioration, or treatment of infectious diseases. More recently, desirable antigens are identified and separated from the whole organism and purified to create subunit vaccines. DNA vaccines use specific genes from the organism that are injected into the animal, thereby causing the animal's cells to produce specific proteins that then induce an immune response.

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

- a) A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian.
- b) There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s).
- c) The practicing veterinarian is readily available for followup in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animals(s) by virtue of examination of the animals(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept.

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.

CVM Mission Statement

The Center for Veterinary Medicine is a consumer protection organization. We foster public and animal health by approving safe and effective products for animals and by enforcing applicable provisions of the Federal Food, Drug, and Cosmetic Act and other authorities.

A Brief History of the Center for Veterinary Medicine

In 1927, The Food, Drug, and Insecticide Administration, later known as the Food and Drug Administration, was formed. The agency employed its first veterinarian, Dr. Henry Moskey, to evaluate vitamins and minerals in light of their claimed nutritional and treatment uses. In 1953, a Veterinary Medical Branch was created in the Bureau of Medicine, then part of the Department of Health, Education, and Welfare (DHEW). In 1965, the Secretary of DHEW established the Bureau of Veterinary Medicine (BVM). By 1984, after many more evolutionary changes, the Bureau of Veterinary Medicine became the Center for Veterinary Medicine (CVM).

Today CVM is an internationally recognized public health organization responsible for the evaluation, approval and surveillance of animal drugs, food additives, feed ingredients, and marketed animal devices. CVM works to increase the availability and diversity of safe and effective products that relieve animal pain and suffering, sustain their health, and improve animal productivity without compromising public health. CVM aligns and utilizes its resources wisely and makes practical use of state of the art science and technologies to best accomplish its mission.

