The US FDA has approved a limited number of treatments for use in food fish. Two commercial aquaculture antimicrobials (oxytetracycline and sulfadimethoxine-ormetoprim combinations) were approved more than 20 years ago. Since these drugs are not effective against all bacteria and are not approved for use in many fish species, additional antimicrobials for use in aquaculture are needed. Because of the expensive drug approval process, pharmaceutical companies have been reluctant to develop new animal drugs for use in aquaculture. Passage of the MUMS Health Act in 2004 has given pharmaceutical manufacturers financial incentives to invest in development of new aquaculture treatments. In addition, increased global demand for farm-raised fish has encouraged farmers to seek effective treatments that will protect their fish crop. Because medicated feeds are easy to administer, fish farmers prefer that additional treatments become available in that form.

Prior to 1996, the FDA’s options for regulating animal drugs were “over the counter” and “by prescription.” At that time, antimicrobials approved for use in aquaculture were marketed as over-the-counter drugs. Public concern regarding issues such as environmental contamination, residues in food, and antimicrobial resistance has prompted the FDA to propose tighter regulations that would require veterinary supervision of drugs used in animal feed. Because of these concerns and because many states prohibited feed mills from dispensing prescription drugs, a coalition of government and industry workers laid the groundwork for the ADAA in 1996. The ADAA is an amendment to section 512(b) of the Federal Food, Drug, and Cosmetic Act that created a new class of therapeutic drugs, the VFD drug. Established in 1996, the VFD is an approval that the FDA may assign to any new antimicrobial for use in or on animal feed. Orders for VFD drugs are available to fish producers only from licensed veterinarians. In 2005, florfenicol became the first VFD drug approved for use in catfish. Veterinary feed directives are a new concept in aquaculture, and specific requirements are needed for veterinarians issuing VFD orders.

Types of animal feed drugs
Medicated animal feeds are classified as category I or II drugs. Category I drugs require no withdrawal period at the lowest concentration at which they are approved for each species. Category II drugs require a withdrawal period at the lowest concentration for which they are approved or are regulated on a no-residue (zero tolerance) basis for at least 1 species. Within each category, there are 3 types of medication: A, B, and C. Type A is any new animal drug used in the manufacture of other medicated articles or type B or C medicated feeds. Type B is a concentrated form of medicated feed used in the manufacture of other medicated feeds. There are restrictions on the concentration of this feed, and it is not to be fed directly to animals. Type C medicated feed is either the final form of complete feed or a supplement to another animal feed. Type C medicated feed is manufactured from a type A medicated article or type B medicated feed. All VFD drugs will be labeled as category II, type A medicated article used to manufacture type B or C medicated feed.

Currently approved VFD drugs
Presently, 2 VFD antimicrobials are commercially available: tilromycin, which is labeled for use in swine feed, and florfenicol, which is labeled for use in catfish feed. Tilromycin was approved in 1996 for control of swine respiratory tract disease, and veterinarians in swine practice are accustomed to issuing VFD orders. Florfenicol was approved in October 2005 as a VFD drug for the control of mortality due to ESC associated with Edwardsiella ictaluri. Numerous other antimicrobials for use in aquaculture, as well as additional label claims for florfenicol, are presently being investigated as investigational new animal drugs (INADs) and could be approved as VFD drugs for treating commercial, recreational, or hobby fish.

Veterinarians and VFD orders in aquaculture
In the United States, few veterinarians are trained in the field of aquaculture, compared with other veterinarians' role in the use of veterinary feed directive drugs in aquaculture
Patricia S. Gaunt, DVM, PhD, DABVT

ABBREVIATIONS
MUMS Minor use and minor species
ADAA Animal Drug Availability Act
VFD Veterinary feed directive
ESC Enteric septicemia of catfish

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nary medical specialties. Although most aquaculture veterinarians are associated with universities and aquaria in large cities, most commercial food fish operations are located in rural areas near diagnostic laboratories served by fewer veterinarians. Fish farmers in rural areas will likely depend on local practitioners in companion or food animal practice to properly diagnose and recommend treatments for fish diseases treatable with VFD drugs. Because extensive courses in aquatic veterinary medicine are not offered at all veterinary colleges, most veterinarians are not adequately trained in disease and diagnostic procedures for fish. For veterinarians interested in aquatic diseases, continuing education courses in aquatic animal medicine are offered at many local and national veterinary meetings as well as fishery meetings. The Southern Regional Aquaculture Center and the Aquaculture Network Information Center (AquaNIC) provide information on fish husbandry, diseases, and treatments. In addition, aquatic veterinarians and fishery extension agents are cooperating to educate veterinary practitioners on diagnostic tests available for fish diseases treatable by a VFD drug.

**VFD regulations that apply to veterinarians**

For a veterinarian to issue a VFD order, a valid veterinary-client-patient relationship must exist. The veterinarian must examine the producer's fish and ascertain that they are ill on the basis of clinical signs, lesions, or results of diagnostic tests such as bacterial culture. If the fish have a bacterial disease that is treatable with a VFD drug and the farmer chooses to use this treatment, the veterinarian will issue a medicated feed order. The VFD order can only be written for treatment of a disease in that fish species for which there is a label claim. Extralabel use of a VFD drug is prohibited by law. Although the active ingredient in the VFD drug may be approved for use in other animal species (eg, florfenicol injectable in cattle), only the approved formulation can be used to manufacture the VFD medicated feed (eg, florfenicol type A medicated article for catfish).

By law, the veterinarian must discuss proper use of the medicated feed, including dose rate, duration of treatment, and withdrawal time. The quantity of medicated feed ordered is based on the weight of the fish in the pond as estimated by the fish farmer from fish stocking and growth rates.

The farmer must agree to use the drug in accordance with VFD regulations as explained by the veterinarian. Either the veterinarian or the farmer may present the original VFD order for filling. The veterinarian will issue a medicated feed order. The VFD order is 15 days from the date of issuance. The approved regimen for treating ESC with florfenicol is a dose rate of 10 mg of florfenicol/kg (4.5 mg/lb) of body weight fed once a day for 10 days. The preslaughter withdrawal time for florfenicol is 12 days.

The feed distributor must retain the original VFD record, and the veterinarian and the fish farmer must each retain a copy of the order for a minimum of 2 years. Although VFD order forms can be faxed, the original order must be received by the distributor within 3 working days. Veterinary feed directive orders cannot be provided to the feed distributor via telephone. The veterinarian, fish farmer, and feed distributor must make VFD records available for review and copying in the event of an FDA inspection.

**Expiration dates, refills, and reorders of VFD orders**

According to regulations of the ADAA, the expiration dates of a VFD order may be extended to medicate multiple production groups and provide efficient treatment of sick animals. However, the FDA reserves the right to regulate expiration dates on a drug-by-drug basis. For florfenicol, the FDA regulations state that the expiration of a VFD order is 15 days from the date of issuance. Although ADAA regulations allow refills of VFD orders at the veterinarian’s discretion, the FDA has mandated that refills are not available for florfenicol. If catfish infected with *E ictaluri* are treated with florfenicol for 10 days and the farmer requests additional treatment of fish in the same pond, a new VFD order must be issued by the veterinarian. Concurrent ESC outbreaks from multiple ponds on 1 farm may be treated with florfenicol on the basis of results of examination of ill fish from a representative pond at the discretion of the attending veterinarian. The veterinarian assumes responsibility and liability for diagnosis of fish in all treated ponds.

**Manufacture of VFD medicated feeds**

Only feed mills that hold a medicated feed mill license and are registered with the FDA can manufacture VFD medicated feeds. A licensed feed mill purchases the drug from its manufacturer, which will sup-
ply any special instructions on mixing the medication with fish feed. Veterinarians are not responsible for supervising the preparation of the VFD medicated feed.

Commercial fish feed is often manufactured in lots of 5 tons or more, rather than on an individual basis. For practical reasons, the feeding rate (calculated as a percentage of body weight) for medicated feed is determined by the feed mill on the basis of local feeding practices.

The percentage feeding rate and dosage will determine the concentration that medication is blended into feed, according to the following formula:

\[
\text{Concentration of medication in feed} = \frac{\text{dose rate}}{\text{percentage feeding rate}}
\]

For florfenicol, the dose rate is 10 mg of active ingredient/kg of body weight and the feeding rate used in the Mississippi Delta is 2% of body weight. Therefore, the drug would be blended as a 500-ppm (500 mg/kg) concentration in fish feed.

The feed mill can manufacture VFD medicated feeds in advance but cannot dispense them without a signed VFD order from a licensed veterinarian. Medicated feeds are typically supplied to fish producers in lots ranging from 25-lb bags to truck loads that weigh several tons. Veterinary feed directive medicated feeds must be clearly labeled with ingredient statements, cautionary statements, and withdrawal information.

**Distribution of VFD medicated feeds**

A distributor is defined as the person or company who sells a VFD medicated feed to a farmer or other distributor. Prior to selling VFD medicated feeds, the distributor must file a one-time notice to the FDA. When the distributor sells the medicated feed to a fish farmer, he or she must retain the original VFD order. If the feed mill serves as the manufacturer as well as the distributor of the VFD medicated feed, the original VFD order will be maintained at the feed mill. A veterinarian can become a distributor of VFD medicated feeds provided that the veterinarian has filed the required notice with the FDA.

**Future outlook**

The Office of MUMS Animal Drug Development was created by the FDA Center for Veterinary Medicine to oversee and facilitate approval of new minor species drugs granted by the MUMS Act. With financial incentives for drug manufacturers, additional VFD drugs will hopefully be available for use in aquaculture. Improved cooperation with extension agents and additional continuing education programs available through veterinary meetings, fish health meetings, and Web sites will be important in helping veterinarians correctly use VFD drugs in fish medicine practice.

**References**


**Appendix**

Information required on VFD order forms.

**References**