

Medicated Feed for Food Fish

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Medicated feed is frequently recommended to control bacterial disease outbreaks in cultured fish. Medicated feeds are commercially prepared, and contain an antibiotic to control specific bacterial infections by either killing the bacteria or preventing the bacteria from reproducing. Antibiotics do not control parasites, fungus, or viruses.

Bacterial disease

Bacterial infections occur in fish just like any other animal. Several different pathogenic bacteria are associated with disease in cultured freshwater food fish such as channel catfish, hybrid striped bass, and salmon. For specific information on bacterial diseases see SRAC Publication No. 477, *ESC - Enteric Septicemia of Catfish*; SRAC Publication No. 478, *Aeromonas Bacterial Infections - Motile Aeromonad Septicemia*; and SRAC Publication No. 479b, *Columnaris Disease: Flavobacterium columnare*.

Fortunately, many bacterial diseases of cultured fish can be successfully treated with medicated feeds that contain U.S. Food and Drug Administration (FDA) approved antibacterial drugs. These compounds have undergone extensive animal, human-food, and environmental testing prior to approval for use in fish. Unfortunately, there are very few drugs approved by the FDA for use in fish in the United States. Compounding this issue can be the improper use of antibiotics which has resulted in development of many antibiotic resistant strains of bacteria. Therefore, medicated feeds should only be used when absolutely necessary and according to label or veterinarian instructions. Because there are so few approved

drugs for use in aquaculture, preventing bacterial disease outbreaks with proper disease management strategies is the best method to avoid bacterial diseases in fish. For more information on preventing diseases on fish farms see SRAC Publication No. 4703, *Disease Prevention on Fish Farms*; SRAC Publication No. 4707, *Biosecurity in Aquaculture, Part 1: An Overview*; and SRAC Publication No. 4708, *Biosecurity in Aquaculture, Part 2: Recirculating Aquaculture Systems*.

Bacterial diseases of fish are usually a result of a stressful event such as periods of low dissolved oxygen or spawning stress. In nature, fish are generally less prone to bacterial disease outbreaks as they can seek the least stressful conditions. In aquaculture, fish often are unable to reduce their own stressful conditions, and thus, are weakened by increased fish density, inadequate nutrition, poor water quality (i.e., low dissolved oxygen or high ammonia and nitrite), parasite infestation, and handling.

When stress occurs in fish, their immune system is suppressed, increasing susceptibility to bacterial infections. As a result, cultured fish are more susceptible to disease than free-ranging animals. Minimizing stressful conditions often reduces the incidence of disease. Failing to correct stressful conditions that lead to a disease outbreak, even while treating sick fish with medicated feed, will usually prevent the medication from being fully effective or will result in a reinfection of disease after treatment is completed. Therefore, medications should only be thought of as part of the strategy in controlling and preventing disease. Prior to and during medication, fish culturists should review all husbandry and environmental factors that may have contributed to the disease outbreak and correct them to prevent the disease from continuing or reoccurring.

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Bacteria are either opportunistic or obligate pathogens. Opportunistic bacteria are present in the water and inside the fish, and generally cause no problem. When culture conditions deteriorate, these bacteria will take the opportunity to cause disease in infected fish. Common examples of opportunistic bacteria which can cause disease and death of food fish include: *Aeromonas hydrophila*, *Flexibacter columnaris*, and *Pseudomonas fluorescens*.

Obligate pathogenic bacteria can cause disease even in the absence of stressors. Examples include *Aeromonas salmonicida*, *Edwardsiella ictaluri*, *Renibacterium salmoninarum*, and *Yersinia ruckeri*. However, they can become more problematic under stressful environmental conditions.

Use of medicated feeds

Once a bacterial infection has been diagnosed in fish, an approved antibiotic feed can be determined. The treatment should always be the maximum recommended dose for that species and should be fed for the total number of days recommended (even if the fish appear to have recovered before the end of the treatment period). Feeding lower concentrations of antibiotics or decreasing the number of days the drug is fed can allow bacterial pathogens to develop a resistance to the antibiotic. If this occurs, the antibiotic would likely not be able to control certain infections that may occur later at a fish farm or hatchery.

Fish often stop eating as a bacterial disease progresses, so early diagnosis and treatment are essential to ensure that infected fish consume the medicated feed. Once a bacterial disease is diagnosed, and the appropriate medicated feed is determined, the feed should be used immediately. Furthermore, doses have been calculated for an antibiotic to maintain a certain level in the bloodstream for a certain period of time in order to be effective. Depending upon the compound, it takes a day or so to reach this level. Treatment should be done for the prescribed time and never stopped prematurely because the fish “look better”.

Prophylactic use of antibiotics is prohibited. Such use can lead to increased disease resistance and higher residues of the antibiotic in the tissues of fish. Prophylactic use of antibiotics has not been shown to increase growth rates in fish. For these reasons, only use antibiotics when absolutely necessary to treat a bacterial infection.

It is important to emphasize to all involved, the proper withdrawal time for the antibiotic used (see Table 1), and that all understand that no food fish harvest will occur prior to that period being completed. This is to

ensure that the antibiotic is out of the fish and that it is safe for human consumption. It is a good idea to designate this date on the pen, tank, or raceway with a clearly visible and prominent sign in order to eliminate any potential error of a premature harvest.

The U.S. Food and Drug Administration (FDA) has approved only four antibiotics for use in food fish. The three antibiotics that are commercially available are **Terramycin®** (Terramycin® 200 for Fish), **Romet®** (Romet®30 and Romet® TC) and **Florfenicol** (Aquaflor®). Sulfamerazine® is also approved but is no longer available. FDA approves specific products that contain the antibiotics and only those specific products can be purchased and used for species listed on the label. For example, if the fish species is not listed in Table 1 for use with Terramycin®, it cannot be legally used to treat the bacterial infection in that species.

Each of the currently approved antibiotics and the approved product is discussed separately below. This list may change as new antibiotics obtain approval for use in food fish. To determine if an antibiotic not on the list below has obtained approval, please visit the FDA Center for Veterinary Medicines website at: <http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/Aquaculture/ucm132954.htm>

Terramycin®

Terramycin® has been used for treatment of food fish for many years. The approved product for fish is Terramycin®200 for Fish, which contains the active ingredient oxytetracycline dihydrate. This drug is usually effective against a number of bacteria which cause disease in food fish (Table 1).

Terramycin® 200 for Fish is incorporated into the feed by commercial feed mills licensed by the FDA. The label (Table 2) includes a feeding rate to achieve the desired dosage levels required to attain adequate therapeutic treatment. Terramycin® must be fed for 10 days to control the infection. Once the treatment is completed, the fish must be held for an additional 21 days before they can be marketed for food or released into the wild in order to allow elimination of the drug from the fish. Marketing fish for human consumption before the end of the 21-day withdrawal period is a violation of federal law. As a result, marketing plans must be considered before treating fish with Terramycin®. Once treated, fish cannot be sold for a minimum of 31 days (10-day treatment period plus 21-day withdrawal period). An additional consideration when feeding Terramycin® medicated feed manufactured at a feed mill is that it is only available as a sinking feed. The drug is broken down by the higher temperatures needed

Table 1: Antibiotics approved for use in medicated feed for foodfish.

Trade name	Species	Indications (For the control of:)	Dosing	Limitations
TERRAMYCIN®200 for Fish	Salmonids	Ulcer disease (<i>Hemophilus</i> spp.), furunculosis (<i>Aeromonas salmonicida</i>), bacterial hemorrhagic septicemia (<i>A. liquefaciens</i>), and pseudomonas disease (<i>Pseudomonas</i> spp.)	2.5 – 3.75 g per 100 lbs fish per day for 10 days	21-day withdrawal time
	Freshwater-raised Salmonids	Mortality due to coldwater disease caused by <i>Flavobacterium psychrophilum</i>	3.75 g per 100 lbs fish per day for 10 days	21-day withdrawal time
	All freshwater-raised <i>Oncorhynchus mykiss</i>	Mortality due to columnaris disease	3.75 g per 100 lbs fish per day for 10 days	21-day withdrawal time
	Catfish	Bacterial hemorrhagic septicemia (<i>A. liquefaciens</i>) and pseudomonas disease (<i>Pseudomonas</i> spp.)	2.5 - 3.75 g per 100 lbs fish per day for 10 days	Water temperature not below 62°F 21-day withdrawal time
ROMET®30 and ROMET®TC	Salmonids	Furunculosis due to <i>Aeromonas salmonicida</i>	50 mg per kg fish per day for 5 days	42-day withdrawal time
	Catfish	Enteric septicemia due to <i>Edwardsiella ictaluri</i>	50 mg per kg fish per day for 5 days	3-day withdrawal time
Aquaflor® (VFD Drug)	Catfish	Mortality due to enteric septicemia associated with <i>Edwardsiella ictaluri</i>	10 mg per kg fish per day for 10 days	15-day withdrawal time
	Freshwater-raised Salmonids	1) Mortality due to furunculosis associated with <i>Aeromonas salmonicida</i> 2) Mortality due to coldwater disease associated with <i>F. psychrophilum</i>	10 mg per kg fish per day for 10 days	15-day withdrawal time
	Freshwater – raised finfish	Mortality due to columnaris disease associated with <i>Flavobacterium columnare</i>	Warmwater 15 mg per kg fish per day for 10 days Others – 10 mg per kg fish per day for 10 days	15-day withdrawal time
	Freshwater-raised warmwater finfish	1) Mortality due to streptococcal septicemia associated with <i>Streptococcus iniae</i>	15 mg per kg fish per	15-day withdrawal time

Table 2: Label rates of Terramycin® 200 for fish to use at various feeding rates.

Feeding Rate			
To achieve a dose rate of 2.5 – 3.75 g/100 pounds of fish			
Pounds feed/ 100 Pounds fish (%)	Terramycin in Finished Feed (g/ton)	Terramycin for Fish per ton of feed (pounds)	Total biomass that one ton of medicated feed will treat (pounds)
1	5,000 – 7,500	25.00 – 37.50	200,000
2	2,500 – 3,750	12.50 – 18.75	100,000
3	1,667 – 2,500	8.33 – 12.50	66,667
4	1,250 – 1,875	6.25 – 9.38	50,000
5	1,000 – 1,500	5.00 – 7.50	40,000
6	833 – 1,250	4.17 – 6.25	33,333
7	714 – 1071	3.57 – 5.36	28,571
8	625 – 938	3.13 – 4.69	25,000
9	556 – 833	2.78 – 4.17	22,222
10	500 – 750	2.50 – 3.75	20,000
15	333 – 500	1.67 – 2.50	13,333

to make a floating pellet. Feeding a sinking food to sick pond fish makes it difficult to determine if they are eating the medicated feed. Terramycin® 200 can be top dressed on floating feeds with vegetable oil, but the stability of the antibiotic on the feed may be inferior to the stability in a manufactured feed.

Romet®

Romet® (Romet-30®, Romet-TC®) is approved for use in salmonids and catfish. This product contains two drugs, sulfadimethoxine and ormetoprim. These drugs in combination are more effective than either drug used alone, with both acting on different parts of the folic acid metabolism pathway. Bacteria need to manufacture folic acid for cell reproduction, where fish and humans can receive theirs from the diet. This makes the compound very safe for animals

Romet® is specifically approved for treatment of bacterial diseases listed in Table 1. Romet® medicated feed is only fed for 5 days as opposed to the 10 days for Terramycin®. The withdrawal period for Romet® is 3 days for channel catfish. With a 5-day treatment period and a 3-day withdrawal period, catfish treated with Romet® can be slaughtered in as little as eight days after the drug treatment is initiated. Salmonids have a required 42-day withdrawal period from Romet® before being slaughtered. Another advantage of Romet® is its availability from commercial mills in a floating pellet. This allows direct pond observation of the fish eating the medicated feed.

Florfenicol

The Veterinary Feed Directive (VFD) is a new category of medicated feeds created by the Animal Drug Availability Act of 1996. It provides an alternative to prescription status for certain animal drugs for use in feed, while requiring participation of a veterinarian to issue a directive to enable producers to acquire VFD medicated feeds. Antibiotics listed under the VFD listing cannot be used as extra label, meaning it cannot be used on fish species other than those listed on the label.

Florfenicol, sold under the trade name of Aquaflor®, is the first antibiotic used in aquaculture that falls within the VFD. This means that florfenicol can only be used under the supervision of a licensed veterinarian in the context of a valid veterinarian-client relationship. Additionally, florfenicol cannot be used under extra-label drug use options unless the producer is using it under an FDA Investigational New Animal Drug (INAD).

Florfenicol is specifically approved for treatment of bacterial diseases listed in Table 1. Florfenicol medicated feed is fed for 10 days. The withdrawal period for florfenicol is 15 days for channel catfish, salmonids raised in freshwater, and warmwater finfish raised in freshwater. As a result, fish cannot be sold for human consumption or stocked into natural waters for 25 days (10 day treatment period and 15 day withdrawal time).

Selecting the proper medicated feed

To optimize the response to medicated feed, the causative agent needs to be identified and a sensitivity test should be performed to ensure that the correct antibiotic is used. A sensitivity test (Fig. 1) shows the relative susceptibility of the disease-causing bacteria to various antibiotics. Small discs, each containing a different antibiotic are placed on an agar plate that has been recently inoculated with the isolated disease causing bacteria. If bacteria are unable to grow in the presence of a particular antibiotic, a clear area is present surrounding the disc. If the drug has no effect, the bacteria will grow up to or over the top of the disc. The clear area is measured and compared to a standard to determine if the antibiotic would be effective in treating the bacterial infection. A fish health professional or disease diagnostic laboratory can perform the sensitivity test for you and recommend an antibiotic to be used.

There are situations when antibiotic treatment may be ineffective. Some disease outbreaks are caused by bacteria that are resistant to particular antibiotics and some bacterial diseases cannot be controlled with currently-approved medicated feed. For example, there are no FDA approved antibiotics currently available that are effective against an active outbreak associated with *Renibacterium*

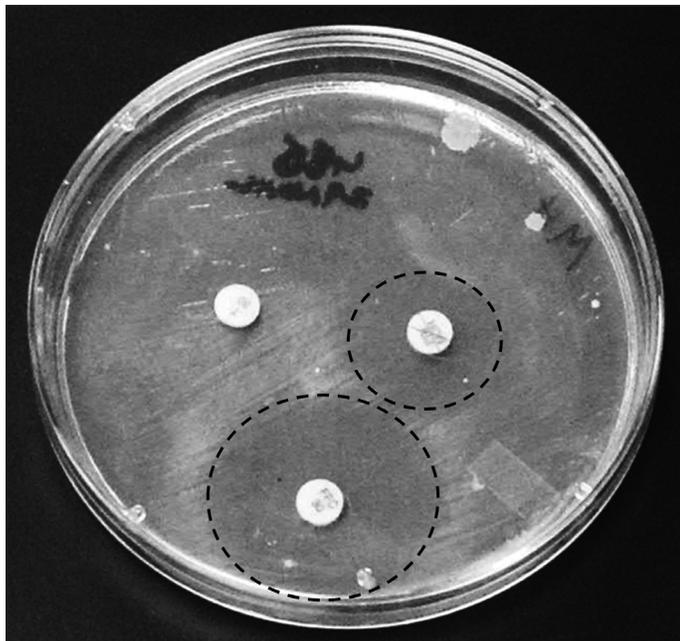


Figure 1. Antibiotic discs on a bacterial plate (white circles). Clear area around the disc (highlighted by the dash lines) indicates that the antibiotic is useful in fighting the infection. Clear areas are measured in millimeters and compared with standards in order to determine if antibiotic is effective against the bacteria disease.

salmoninarum, which is the cause of bacterial kidney disease in salmonids, or *Mycobacterium* species, which can occur in many food fish species including salmon and hybrid striped bass. This is why it is important to work with a fish health specialist/fish veterinarian for proper diagnosis.

Treatment strategies

Economics and other factors also help to determine the appropriateness of using medicated feed. If the cost of the treatment is more than the cost of the fish, it does not make economic sense to treat the fish. When possible, expensive treatments should be avoided unless they are likely to save money for the producer. A good example is the treatment strategy for Enteric Septicemia of Catfish (ESC) caused by *Edwardsiella ictaluri*. This disease occurs when temperatures are between 68 and 82 °F (20 and 28 °C) when the bacteria are in their optimum growth range. Fish dying from ESC will usually stop dying as temperatures rise above 82 °F (28 °C) or fall below 68 °F (20 °C). Medicating fish just before temperatures are forecast to be in the 90s, for example, is often not advised, because the disease stops on its own due to the high temperatures. Using this type of strategy can save a significant amount of money on medicated feed purchases.

Mixing medicated feeds

All of the approved antibiotics for use in food fish are Type A medicated feeds. Producers may purchase Type A premixes only if they hold a valid feed mill license. The VFD form issued by the veterinarian will contain mixing or dilution instructions. Medicated feed mill license applications (Forms FDA 3448) may be obtained from the Public Health Service, Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20785, or electronically from the Center for Veterinary Medicine home page at <http://www.fda.gov/cvm>. Additionally, a set of guidelines for manufacturing feed, referred to as Good Manufacturing Practices (GMPs), are designed to prevent feed contamination and provide reasonable assurance that medicated feed additives are used properly. These guidelines serve as Food and Drug Administration (FDA) regulations. Everyone involved in producing medicated or non-medicated feed, whether at a commercial off-farm plant or with an on-farm mill or grinder/mixer, must comply with the GMPs.

Storage of medicated feed

As with all fish food, medicated feed should be stored in a cool, dry place. If available, a freezer is ideal for storing fish feed for extended periods provided it does not get moist or wet. Antibiotics and essential nutrients will deteriorate rapidly in a warm, moist environment. Excessive decomposition of antibiotics as a result of improper storage can result in unsuccessful treatment. Any unused medicated feed, stored at room temperature, should be discarded after 3 to 4 months. However, a VFD medicated feed is not valid 5 days after the prescribed treatment terminates. Thus florfenicol (Aquaflor®) is a one-time use purchase and any extra feed must be discarded and not kept for future use. Be sure to follow all state guidelines for disposal of unused or old medicated feed.

Use of medicated feed in alternative species

At the time of this writing, FDA will allow veterinarians to prescribe the use of Terramycin® 200 for Fish and Romet®30 or Romet® TC medicated feed for fish species or diseases other than those listed on the label. For example, Terramycin® 200 for Fish, medicated feed that has been approved for use in catfish, may be prescribed extra-label for hybrid striped bass by a licensed veterinarian. Florfenicol (Aquaflor®) cannot be legally used on species other than those on the label, unless it is used under an INAD. Check with a qualified fish health professional or veterinarian on the current status of medicated feed use regulations before treating your fish.

Additional information on use of medicated feeds approved for use in food fish can be found at:
<http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/Aquaculture/ucm132954.htm>
<http://www.fws.gov/fisheries/aadap/home.htm>
Quick Reference Guide to Approved Drugs for Use in Aquaculture. 2011. http://www.fws.gov/fisheries/aadap/PDF/Flip-book_FINAL%20for%20web%2023may2011.pdf.

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