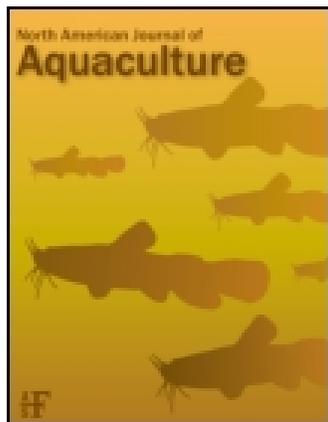


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Mythbusters: What's Real and What's Not When It Comes to Fish Drugs

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SPECIAL SECTION: HaMAR

Mythbusters: What's Real and What's Not When It Comes to Fish Drugs

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Abstract

Successful fish culture programs take a comprehensive approach to disease management, broodstock conditioning and spawning, marking progeny, and reducing handling stress. Occasionally, drugs are needed to facilitate these tasks, and the only drugs legally available are those that have been approved for such use by the U.S. Food and Drug Administration. A lack of understanding of the approval process and how these products are actually used in fish culture has led to unfounded concerns regarding potential human health issues, unsafe drug residue levels in fish stocked into public waters, and the discharge of elevated concentrations of drugs in hatchery effluents. The rigorous drug approval process requires extensive data to demonstrate that a drug is safe and effective for fish as well as safe to humans and the environment, that it is manufactured and packaged properly, and that it is labeled to avoid misuse. Further, the approval process assumes a naive user and is structured to ensure that, if a drug is approved, even inexperienced personnel could be expected to apply it safely and effectively. If inexperienced personnel can apply these products successfully, experienced fisheries professionals certainly can. In this paper, concerns and misconceptions regarding the drug approval process and use of drugs in fish culture are addressed from a fishery biologist's perspective.

Meeting fisheries management goals, fish production goals, and research objectives often requires the administration of drugs to treat infections or infestations, induce spawning, facilitate handling or surgical procedures, or mark fish to distinguish hatchery-origin fish from wild fish. Whether it involves sedating fish for weighing and measuring in the field or controlling a bacterial infection in the hatchery, virtually every fisheries science or conservation program relies upon the availability of safe and effective fish drugs. The U.S. Food and Drug Administration (FDA), which is part of the U.S. Department of Health and Human Services, is responsible for protecting and promoting public health by various means, including regulating the development and use of animal drugs. Although the FDA has

classified fish as a “minor species,” they are nonetheless considered food animals and the administration of drugs to them must be in accordance with the Federal Food, Drug, and Cosmetic Act (FFD&CA [passed in 1938]) and FDA regulations. The use of fish drugs is plagued by confusion and misconceptions. What, exactly, is a fish drug? Why are they used? How do we know they are used safely and judiciously? In spite of the fact that virtually all fisheries professionals advocate legal and judicious use of drugs and apply them accordingly, uninformed off-hand remarks and popular media occasionally suggest otherwise.

In this paper, concerns and misconceptions regarding the drug approval process and the use of drugs in fish culture are addressed from a fishery biologist's perspective. The focus is

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on therapeutic drugs (e.g., antibiotics, antimicrobials, and antiparasitic compounds) and sedatives/anesthetics, as these are the types of drugs most commonly used in fish culture and those applied to fish that may be subsequently released to the wild or directly consumed. Although spawning aids (hormonal treatments) are an important class of drugs used in aquaculture, they are primarily applied to broodstock (i.e., fish that are not released or consumed) and are outside the scope of this paper. Similarly, drugs are essential tools in the culture of imperiled species (i.e., the propagation of species protected under the Endangered Species Act), but the nuances of drug application in these circumstances are beyond the focus of this work.

WHAT IS A DRUG AND HOW IS ONE APPROVED?

Only drugs approved by the FDA have been proven to be effective and safe to fish, human consumers, and the environment and are therefore legal to use on fish in the United States (USFDA 2013). The FDA defines a drug as (1) a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and (2) a substance (other than food) intended to affect the structure or any function of the body. The FDA further recognizes as drugs (1) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of these, or (2) articles intended for use as a component of any articles specified above (Federal Food, Drug, and Cosmetic Act 2010). By this all-inclusive definition, compounds such as ice (which is used to reduce the metabolic rate of fish during transport) and salt (sodium chloride, which used as a parasiticide and as an osmoregulatory aid to reduce stress) are considered drugs. Many other innocuous compounds, like fuller's earth (used to reduce the adhesiveness of fish eggs), sodium bicarbonate (used to introduce carbon dioxide into the water for anesthetizing/sedating fish), and hydrogen peroxide (used as a bactericide and parasiticide) are also considered drugs. It should be noted that the term "drug" does not necessarily mean "antibiotic," though antibiotic products would certainly fall under the FDA definition of drug. Although the distinctions are nuanced, there are some products/product applications that are either not considered to be drugs/drug applications or that fall outside the regulatory authority of the FDA. Examples include veterinary biologics (i.e., vaccines, bacterins, and related products), which are regulated by the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture, and chemicals (e.g., disinfectants, sanitizers, and herbicides), which are used exclusively for the control of algae or other nonpathogenic pests and which are regulated by the U.S. Environmental Protection Agency. This paper will focus on use of drugs in fish culture; for more information about these other products/product applications, see the *Guide to Using Drugs, Biologics, and Other Chemicals in Aquaculture* (Bowker et al. 2014).

Historically, fisheries professionals were not restricted to using only FDA-approved fish drugs. Although the FFD&CA made all uses of unapproved animal drugs illegal, from 1938 to 1994 the FDA did not exercise its regulatory authority over the use of drugs in fish culture. Effectively, this meant that there were few limitations on the kinds of products that could be used to treat fish. In 1994, the FDA began to enforce the FFD&CA and issued regulations regarding the use of drugs in aquatic species. This meant that all new fish drugs were scrutinized under the New Animal Drug Application (NADA) process before approval, and surveillance and compliance inspections of fish culture facilities were initiated. Fisheries professionals who do not use fish drugs legally may violate FFD&CA provisions stipulating that (1) the use of an unapproved new animal drug is "unsafe," (2) the presence of an unsafe new animal drug in food causes it to be adulterated, (3) a new animal drug is also unsafe if its use does not conform to its approved application, (4) the presence in food of a residue of a new animal drug above the established tolerance causes the food to be adulterated, and (5) the introduction or delivery for introduction into interstate commerce of any food that is adulterated is prohibited.

To the credit of the fisheries profession, very few of these types of violations have been uncovered. This has allowed the FDA to focus their resources on noncompliance matters, but with the caveat that surveillance and compliance inspections could increase at any time if violations warranted such action. The small number of violations is especially commendable given the very limited number of drugs that are currently approved by the FDA. Although most of the drugs used by fisheries professionals prior to 1994 had been used safely and effectively for decades, the vast majority of these drugs were not FDA approved and their continued use could have had serious legal ramifications. When implemented, FDA's new enforcement priorities effectively stripped fisheries professionals throughout the country of virtually all the tools that had been used for decades to manage fish health and achieve fish culture, fisheries management, and fisheries research goals. These logistical constraints jeopardized recreational fishing opportunities, restoration/conservation programs, and commercial production efforts across the nation, threatening to have significant economic impact (Schnick 2001; Trushenski et al. 2013).

The NADA process is a stringent, science-based regulatory review overseen by veterinarians, animal and environmental scientists, chemists, and biologists/toxicologists who work in the FDA's Office of New Animal Drug Evaluation within the Center for Veterinary Medicine (CVM). Before a new drug can be approved for use with fish, it must be proven effective and safe to fish, the environment, and to consumers of treated fish. These are appropriate metrics and, on its face, the approach seems sensible and straightforward. However, the FDA uses a precautionary approach for fish drug approvals, and demonstrating safety and effectiveness is an involved and exhaustive process requiring the preparation of extensive data sets according to strict research protocols (e.g., Trushenski et al. 2013). As a result, new

fish drug approvals have been limited by the complexities of the FDA regulatory framework, the lack of economic incentives for pharmaceutical companies (sponsors) to pursue approvals for fish drugs, and the absence of the centralized expertise needed to shepherd promising fish drugs through the approval process. Confounding this issue is the fact that more than 100 species of freshwater fish are reared in the United States under variable environmental conditions, and the FDA generally requires that as many as six different fish species be tested for approval to use a drug in all freshwater finfish (there are no drugs currently approved for use in marine fish; the data requirements for such approvals are unclear at this time). Gaining approval for the use of a drug on a major species (horses, dogs, cats, cattle, pigs, turkeys, and chickens) is considerably easier, in that studies are typically required for just one breed. Because of the prohibitive cost of a new fish drug approval and the fact that there is minimal economic incentive to invest the exorbitant amount of money needed to gain such approval, drug sponsors rely heavily upon public partners (federal and state agencies, universities, etc.) to generate the majority of the data required for a new approval. For the most part, the public partners are researchers involved in fish culture/fish health that have a vested interest in the health and well-being of fisheries in the United States. In short, the absence of fish drugs does not reflect the lack of need for these tools or, in many cases, the nature of the drugs themselves; rather, limited access to fish drugs primarily reflects the laborious, time- and resource-consuming drug approval process. Recognizing this problem, the FDA established the Minor Use/Minor Species Grant Program to support the development of new animal drugs intended for use in minor species or minor uses of major species. The FDA is authorized to provide grants for designated new animal drugs to assist in defraying the costs of qualified safety and effectiveness testing. In spite of the fact that there are few drugs legally approved for use in aquaculture and a major regulatory agency is responsible for drug use compliance oversight, there are common myths perpetuated by some that are not substantiated by scientifically valid data.

MYTH I: HATCHERY FISH ARE “FESTOONED” WITH DRUG RESIDUES

A recent article claimed that “[a]quaculture is so festooned with antibiotics, veterinary drugs, and pesticides, it can make factory farming look, well, green” (Rosenberg 2013). Online opinion pieces like this one can be readily dismissed as uninformed commentary, but they are representative of a broader misunderstanding: without having the slightest notion as to how, why, or even whether it is true, the general public simply “knows” that cultured fish are burdened with drug residues. As it happens, there are no scientifically valid, statistically defensible data to support such claims, and yet the myth is pervasive. It is unsettling for those involved in fish drug approval efforts to hear such claims, particularly the staff at CVM

whose job involves ensuring that the fish that are treated with drugs are wholesome and healthy and do not present a risk to consumers.

Before a drug is approved, a considerable amount of work must be done to identify and assess the depuration of drug metabolites in various fish tissues during and after treatment. These studies use highly sensitive analytical methods to assess pharmacokinetics and monitor drug residue depletion in order to establish appropriate withdrawal periods, i.e., the amounts of time that fish must be held following drug treatment before they are harvested for consumption or released to the wild (where they may be caught by anglers or commercial fishing operations and subsequently consumed). Because fish are poikilotherms, residue depletion studies are conducted at the lowest practical water temperature to approximate a worst-case scenario for drug depuration. Thus, withdrawal periods are established using inherently conservative approaches to ensure that treated fish do not enter the food supply until they are safe for consumption. Virtually all of the residue depletion data generated to support a fish drug approval, as well as data demonstrating that a drug is as effective as claimed, is safe to the fish, and is safe to the environment, are made publically available by the FDA.

For example, the current tolerance for florfenicol residues is 1 ppm (measured as florfenicol amine) in catfish muscle and salmon muscle/skin. Kosoff et al. (2009) showed that 14 d after applying Aquaflor (50% florfenicol) according to the proposed treatment regimen, florfenicol residues in skin-on fillets were ≤ 0.3 ppb in Nile Tilapia *Oreochromis niloticus* (held at 25°C or 30°C), Walleye *Sander vitreus* (20°C or 25°C), and sunshine bass (female White Bass *Morone chrysops* × male Striped Bass *M. saxatilis*; 20°C or 25°C). Similarly, Gaunt et al. (2012) reported that the concentration of florfenicol in Channel Catfish *Ictalurus punctatus* plasma dropped below the detection level 96 h after the treatment regimen was completed. Accordingly, the withdrawal period for Aquaflor was established as 15 d. The tolerance for oxytetracycline (OTC) residues in food is 2.0 ppm. Chen et al. (2004) showed that OTC residues in skin-on fillets of sunshine bass, Nile Tilapia, Summer Flounder *Paralichthys dentatus*, and Walleye fell below this level 11 d after treatment, and the withdrawal period for OTC dehydrate was subsequently set at 21 d. The tolerance for chloramine-T (as para-toluenesulfonamide) is 0.9 ppm in the muscle/skin of all freshwater-reared finfish. Meinertz et al. (2004) reported that para-toluenesulfonamide decreased to ≤ 127 ppb in the skin-on fillet tissue of sunshine bass, Rainbow Trout, and Yellow Perch *Perca flavescens* within 48 h posttreatment. Given this very rapid depuration to levels well below the tolerance limit, there is no withdrawal period associated with the use of chloramine-T. The tolerances for sulfadimethoxine and ormetoprim (the active ingredients of Romet-30) are not included in the Freedom of Information Request summaries posted on the FDA Web site. Regardless, Kosoff et al. (2007) conducted a study to monitor sulfadimethoxine and ormetoprim residues in Nile Tilapia,

Summer Flounder, and Walleyes after administering the standard therapeutic dose for 10 d and found that (1) neither component could be detected in samples of the edible portion of Walleyes (muscle plus skin) collected on day 10 posttreatment or thereafter, (2) only one Summer Flounder had a detectable concentration of either component on day 21 or thereafter, and (3) the elimination of Romet-30 by Nile Tilapia was extremely rapid. Similar results have shown that drug residues accrued after administration of the standard treatment regimen deplete very quickly (i.e., within hours to days) from fish tissues, including blood plasma, kidney, and muscle (e.g., Allen 1988; Xu 1994; Zhang and Li 2007; Bowser et al. 2009; Gaikowski et al. 2010). The withdrawal period for Romet-30 is as long as 42 d, depending on the use pattern.

Commercial producers who harvest fish for human consumption are required by law to adhere to withdrawal periods established by the FDA before fish can be harvested (see FCS 2014 for the withdrawal periods established for approved drugs and Investigational New Animal Drugs [INADs]). As noted above, these withdrawal periods are established using a very conservative approach, considering the rapid rate of depuration observed in the aforementioned studies. The majority of fish that are reared for recreational fishing or restoration/conservation that are treated with a fish drug are reared in a hatchery at an early life stage and are not catchable for weeks to years. Nonetheless, these operations are also subject to the same withdrawal times established during the drug approval process. Based on these scenarios, it is difficult to find scientific support for the comment that hatchery fish are “festooned” with drugs. In addition to the aforementioned FDA regulatory oversight of drug use in fish culture, Fry et al. (2014) identified nine other federal laws (e.g., the Magnuson–Stevens Fishery Conservation and Management Act and the Ocean Dumping Act) which could be used to address antibiotic use and/or food safety in offshore aquaculture (i.e., aquaculture in U.S. federal waters).

Despite the safeguards in place to prevent human exposure to drug residues in farmed fish, drug residues are occasionally detected in the seafood supply. In a recent review of seafood drug residue inspections in Canada, the European Union, Japan, and the United States, Love et al. (2011) reported that these countries’ domestic and imported seafood inspection programs detected a relatively small number of violations; in the United States, FDA seafood inspections from 2001 to 2006 detected a total of 138 violations, corresponding to less than 0.1 violations per 10,000 tons of edible seafood per year. During this time frame, domestic seafood (including aquaculture production subject to the aforementioned FDA regulatory oversight regarding drug use) represented only 10% of the violations detected; a vast majority of violations were associated with seafood imported from Vietnam, China, and, to a lesser extent, Indonesia. In a screening of various seafood types (predominantly farmed fish and shrimp) available in the American Southwest for 47 different antibiotic residues, researchers detected only 5 of these compounds, each at a level well below the established safety

limit for human foods; the report concluded that the antibiotic residue–related human food safety risk associated with seafood consumption in the United States is low (Done and Halden 2015).

MYTH II: DRUG-LADEN WATER IN HATCHERY EFFLUENT AFFECTS THE ENVIRONMENT

Another prevalent myth relates to the fate of waterborne drugs, i.e., the concern that fish culture operations will discharge drug-laden water into the environment. Before an aquaculture drug is approved by the FDA, an environmental assessment (EA) must typically be submitted by or on the behalf of the sponsor. The EA will be reviewed by the CVM Environmental Safety Team, who will determine whether the drug is likely to have any environmental impacts when used for its intended purpose. This evaluation is based on the results of a battery of tests, including (1) environmental fate tests to assess the degradation, mobility, and persistence of the drug and (2) acute and chronic toxicity tests to assess its impact on the survival, growth, and reproduction of algae, aquatic invertebrates (e.g., *Daphnia magna*), and fish.

Most fish drugs have been shown to be safe for the environment, and there are no restrictions on drug use or disposal (e.g., effluent discharge). However, to discharge effluents into U.S. waters, a facility must hold a National Pollution Discharge Elimination System (NPDES) permit and be subject to either self-monitoring (whereby pollutant discharge data are provided to the regulatory authority) and/or monitoring by the U.S. Environmental Protection Agency (EPA) (or the state-level equivalent) to ensure compliance with the permit’s allowances and all other relevant standards set by the regulatory agency. Effluent discharge regulations were substantially strengthened in 2004, when a new effluent rule was adopted for aquatic animal production facilities (hatcheries and fish farms) producing more than 100,000 lb of fish annually (USEPA 2012). The new rule subjected these facilities to more stringent reporting and compliance activities that are primarily intended to reduce the release of solids as well as discharge of drugs and other chemicals. In addition to preapproval assessments of the environmental effects of drug discharge by the FDA and postapproval oversight of drug discharges and compliance matters by the EPA (or the state-level equivalent), a number of federal laws apply to the use and discharge of drugs in federal waters by offshore aquaculture operations (Fry et al. 2014).

In a few cases, the FDA has developed a water quality benchmark for an aquaculture drug, which is similar to the water quality criteria that the EPA (or its state-level equivalents) sometimes derive for chemicals and contaminants. The water quality benchmark may be used by state or federal effluent (NPDES) permitting authorities to determine the need for effluent discharge limits for a drug on a facility-by-facility basis. Such discharge limits are established by taking into account the drug’s toxicity, local discharge conditions (e.g., the amount of dilution),

the type of receiving water (river, lake, or ocean), and other local factors. If a discharge limit is deemed necessary, the effluent permitting agency (either the EPA or a state-level equivalent, depending on which agency has primacy in the state in which the facility is located) is responsible for setting and enforcing this limit.

As noted above, most drugs are not subject to discharge restrictions because, given the relatively small volume of waterborne drugs applied and the low concentrations used, they are not considered to be harmful to the environment. For example, chloramine-T, a drug commonly used to treat external pathogens in fish, is approved for use at concentrations of 10–20 mg/L for short-term treatments (up to 60 min), which are then diluted substantially prior to discharge. Chloramines are also used to disinfect drinking water, and the residual concentration allowed in drinking water (4 mg/L) is only slightly lower than the concentrations approved for therapeutic use in fish culture (USEPA 2013). Although antibiotics are known to have a number of adverse or potentially adverse effects in aquatic environments, a recent review indicated the “contribution of the aquaculture sector is not expected to be a significant percentage of the nonhuman use of antimicrobials in the USA” (Kümmerer 2009).

MYTH III: DRUGS ARE COMMONLY OVERUSED IN AQUACULTURE

Fish drug use at a hatchery or in the field is an extra expense. Many drugs are approved for use in terrestrial food animals not to cure sick animals but to promote growth and enhance “feed efficiency,” that is, to increase the animal’s weight gain per unit of feed (USFDA Green Book 1989). No drugs are approved for such use in fish (USFDA Green Book 1989). Antibiotics are also regularly added to the feed and water of terrestrial animals that are not sick in order to prevent diseases caused by overcrowded and unsanitary conditions (prophylaxis). These nontherapeutic uses translate into greater production efficiencies and lower production costs for many types of terrestrial animal agriculture. However, there is little to no evidence that the use of antibiotic feeds promote feed efficiency in fish (He et al. 2014). In addition, no fish drug has been approved for use to prevent a disease, and there are no drugs in the approval pipeline intended for prophylactic use. Fish culturists use therapeutants to control mortality or reduce pathogen density. Although some therapeutants are available over the counter (e.g., hydrogen peroxide and oxytetracycline dehydrate), others are only available through a veterinary feed directive signed by a licensed veterinarian (e.g., florfenicol). Aquaculturists can little afford to incur additional costs of rearing fish, so administering fish drugs when they are not needed is considered a waste of money, particularly when the evidence of antibiotic-related growth promotion in fish is sparse and equivocal (He et al. 2014). For example, at current prices it would cost US\$35 to treat a relatively small cement raceway (18.3 m × 1.8 m with a water depth of 0.9 m) for 60 min/d for

3 d with 20 mg/L HALAMID Aqua (chloramine-T) and \$73 to administer the same treatment with 50 mg/L 35% PEROX-AID (hydrogen peroxide; Bowker et al. 2013). Another example is that there is a cost increase of \$7.50–\$30 per 50 lb bag of feed to top-coat the feed with one of the FDA-approved antibiotics (at current prices). Simply put, nontherapeutic application of antibiotic drugs is prohibited in the United States, costly, and ineffective; consequently, there is little interest in such practices among North American fish culturists (Alderman and Hastings 1998), and drugs are only administered when absolutely necessary.

MYTH IV: A DRUG CAN BE USED ON FISH BECAUSE IT IS GENERALLY RECOGNIZED AS SAFE FOR OTHER USES AND, AS A RESULT, VARIOUS PRODUCTS ARE USED IN FISH CULTURE WITHOUT OVERSIGHT

There is also misinformation regarding the legality of using drugs on fish that have been designated by the FDA as “generally recognized as safe” (GRAS) for other purposes. Under sections 201(s) and 409 of the FFD&CA, any substance that is intentionally added to food is a food additive, which is subject to premarket review and approval by the FDA unless the substance is generally recognized—among qualified experts—as being safe when used for a particular purpose. Clove oil and some of its components (eugenol, isoeugenol, and methyleugenol) are GRAS for use in dental cement and as food additives. However, neither clove oil nor any of its components are GRAS for use as a fish sedative or anesthetic in the United States or Canada. Thus, while considered GRAS for some applications, clove oil and its constituents are not considered GRAS for use in fish culture and such applications are not legal. Some fisheries professionals are under the impression that if a compound is GRAS for one purpose, it must be GRAS for all purposes and there should be no issue with using clove oil to sedate fish. As a result, the FDA published *Guidance for Industry Document #150: Concerns Related to the Use of Clove Oil as an Anesthetic for Fish* (USFDA 2007), which reminds readers that neither clove oil nor any of its components are the subject of an approved new animal drug application and, because of safety concerns, should not be used as an anesthetic or sedative in fish.

More recently, FDA staff published an article in *Fisheries* (USFDA 2013) entitled “FDA Answers Your Questions about Fish Drugs” that covers topics such as (1) what a drug is, (2) what an approved new animal drug is, (3) what FDA’s approval provides, (4) what the difference between a finished drug product and an active ingredient is, and (5) what the difference between an approved new animal drug and a drug that has an INAD exemption is. The fact that the FDA considers innocuous compounds with GRAS status for use in human foods to be as yet unproven and therefore not necessarily safe for use as aquaculture drugs illustrates the rigor (and occasional idiosyncrasies) of the approval process and the lengths to which the FDA goes

to ensure the safety and effectiveness of an aquatic animal drug before approval is granted.

MYTH V: ONCE A DRUG HAS BEEN APPROVED, IT CAN BE USED FOR ANYTHING AND ANY VERSION OF IT CAN BE USED

Currently, only nine drugs are approved for use on fish (Table 1) and the shortage of FDA-approved drugs is primarily the result of the vast amount of data needed for an approval. Storey (2005) correctly state that (1) significant economic burdens frustrate attempts to add more fish drugs to the medicine chest, (2) under the best of circumstances, the financial investment required to obtain approval of a New Animal Drug Application is substantial, (3) a new animal drug approval can cost over \$40 million, and (4) when the drug product is already legally marketed in the United States, the addition of a new animal species to an existing drug label has been estimated to cost \$2–8 million. Data must be generated to prove (1) that the drug (or its major metabolite) was safe and effective in a suite of mammalian toxicology studies, (2) that drug residues deplete to levels below tolerances established by the FDA, (3) that the drug is safe to discharge into the environment (if it is not, a benchmark has to be established and discharge limits set by the EPA or the state Department of Environmental Quality, whichever has primacy), (4) that there is an adequate margin of safety associated with treating fish at the highest proposed efficacious dosage, (5) that the drug is as effective as claimed, and (6) that the drug can be manufactured consistently at the advertised purity without contamination. Target animal safety and residue depletion studies must be conducted in compliance with Good Laboratory Practices (USOFR 1999), and laboratories conducting these studies will likely be inspected by FDA field inspectors at some time during the approval process.

Although it seems difficult to understand how it could cost so much to get a fish drug approved, it becomes clear when FDA Guidance for Industry documents are read carefully and during the first product development meeting that a sponsor has with CVM to discuss the plan to obtain FDA approval of their product. For example, the suite of studies that may be required to prove that a drug or its chief metabolite is safe to humans may include (1) a battery of genotoxicity studies to assess whether damage to genetic information occurs within a cell that could cause mutations, (2) 90-d subchronic oral toxicity studies in rodents and nonrodents, (3) a teratology study to evaluate abnormalities of physiological development, (4) a two-generation reproduction study, (5) a chronic study, and (6) a carcinogenicity study. These studies are typically done by contract laboratories that conduct biomedical research in support of human drugs and therefore charge amounts that fish drug sponsors find exorbitant.

After a sponsor has made the financial and time commitments needed for a drug approval, it is incumbent on all fisheries professionals to use the drug judiciously. There are numerous sources that provide detailed information about the judicious use

of drugs, particularly antimicrobials, but fisheries professionals should also pay particular attention to preventive strategies, including ensuring appropriate husbandry and culture conditions, performing routine monitoring, and using pre- or probiotics, nutraceuticals, or biologics where appropriate (Bowker et al. 2014). When therapeutic drug treatment is necessary, judicious use should entail use under the direction of a fisheries or fish health professional or veterinarian and accordance with the instructions on the label. If a drug is not available for legal use or is not used judiciously, then other disease management strategies need to be considered. Failure to do so can have far-reaching ramifications, including the increased likelihood of antimicrobial resistance and federal surveillance and compliance inspections.

Many purchasing agents at state and federal agencies are required to purchase the least expensive product when an acquisition request comes across their desk. This has led to the purchase of products that are not approved but that have the same active ingredient as the approved product. This problem was brought to the attention of the CVM, and they took the proactive step of posting a letter addressed to fisheries professionals on their Web site (<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm324048.htm>) stating that (1) not all drugs currently marketed for food fish (fish that will enter the human food supply) are approved and (2) even if a marketed product has the same active ingredient as an FDA-approved drug, that does not mean it is also FDA-approved. Only FDA-approved drugs can legally be used (according to the label claim) on fish in the United States.

One allowable exception to this rule is the use of unapproved drugs under a compassionate INAD exemption, such as those held by the U.S. Fish and Wildlife Service under the National INAD Program. Such exemptions are granted by CVM to permit the purchase, interstate shipment, and compassionate use of unapproved animal drugs for investigational purposes while data are generated for approvals. The National INAD Program allows fish culturists, many of whom are state and federal employees working with threatened or endangered populations, to use investigational drugs to maintain fish health and fish populations and to prevent suffering or death. The INAD program is based on accountability, including for the receipt and use of an INAD and effectiveness trial results, which are ultimately submitted to and reviewed by CVM.

Licensed veterinarians may also write prescriptions for “off-label” (i.e., unapproved) uses of some approved drugs (off-label use is not currently allowed for drugs that are approved under veterinary feed directives, such as florfenicol, even with veterinary oversight), but in doing so they assume all responsibility for establishing effective treatment regimens, appropriate withdrawal times, and the potential for treated animals to enter the human food supply chain. With some notable exceptions, most veterinarians have not received training in fish pathology and are unfamiliar with disease treatment in fish culture. Consequently, most of these professionals are unwilling to prescribe approved drugs for off-label uses in aquaculture.

TABLE 1. Drugs approved by the U.S. Food and Drug Administration for use in fish culture. Reproduced with permission from Bowker et al. (2014); see also USFDA (2014).

Compound	Indication (purpose)
AQUAFLO Active ingredient: 50% florfenicol	Control mortality due to enteric septicemia associated with <i>Edwardsiella ictaluri</i> in catfish Control mortality due to streptococcal septicemia associated with <i>Streptococcus iniae</i> in all warmwater finfish Control mortality due to columnaris disease associated with <i>Flavobacterium columnare</i> in all freshwater-reared finfish Control mortality due to furunculosis in freshwater-reared salmonids Control mortality due to bacterial coldwater disease in freshwater-reared salmonids
35% PEROX-AID Active ingredient: 35% hydrogen peroxide	Control mortality due to saprolegniasis in all freshwater-reared finfish eggs Control mortality due to bacterial gill disease in freshwater-reared salmonids Control mortality due to external columnaris disease in coolwater finfish and Channel Catfish
Chorulon Active ingredient: chorionic gonadotropin	Improve spawning function in male and female brood finfish
HALAMID AQUA Active ingredient: 100% chloramine-T	Control mortality due to bacterial gill disease in freshwater-reared salmonids Control mortality due to external columnaris disease in Walleyes and warmwater freshwater finfish
Parasite-S	Control external protozoa in all finfish
Formalin-F	Control monogenetic trematodes in all finfish
Formacide-B	Control fungi of the family Saprolegniaceae in all finfish eggs
Paracide-F	Control protozoan parasites in penaeid shrimp
Active ingredient: formalin	Control external protozoa in salmon, trout, catfish, Largemouth Bass <i>Micropterus salmoides</i> , and Bluegills <i>Lepomis macrochirus</i> Control monogenetic trematodes in salmon, trout, catfish, Largemouth Bass, and Bluegills Control fungi of the family Saprolegniaceae in salmon, trout, and esocid eggs
Romet 30 and Romet TC Active ingredients: sulfadimethoxine and ormetoprim	Control furunculosis in salmonids Control enteric septicemia in catfish
Pennox 343 Active ingredient: oxytetracycline hydrochloride	Mark skeletal tissues in finfish fry and fingerlings
Terramycin 200 for Fish Active ingredient: oxytetracycline dihydrate	Control ulcer disease, furunculosis, bacterial hemorrhagic septicemia, and pseudomonas disease in salmonids Control mortality due to coldwater disease in freshwater-reared salmonids Control mortality due to columnaris disease in all freshwater-reared Rainbow Trout <i>Oncorhynchus mykiss</i> Control bacterial hemorrhagic septicemia and pseudomonas disease in catfish Control gaffkemia in lobsters
Tricaine-S (commonly called MS-222) Active ingredient: tricaine methanesulfonate	Temporarily immobilize fish of the families Ictaluridae, Salmonidae, Esocidae, and Percidae (in other fish and cold-blooded animals, the drug should be limited to hatchery or laboratory use)

RECOMMENDATIONS FOR FUTURE USE OF FISH DRUGS

As the role of fish hatcheries expands and changes, it is crucial that FDA-approved fish drugs be available and that fisheries

professionals know how to use them in a judicious and legal manner. The factors that should be taken into consideration include (1) the relevance of hatcheries in the future, (2) how external factors such as climate change may affect aquatic animal

health, (3) how fisheries professionals will deal with emerging diseases, i.e., whether the meagerly stocked medicine chest will be sufficient, and (4) whether hatcheries will be able to access and discharge water at current volumes. History suggests that successful fish culture programs take a comprehensive approach to disease management, broodstock conditioning and spawning, marking progeny, and reducing handling stress. Administration of a fish drug may be required to accomplish each of these tasks, and consideration should be given to whether there is an FDA-approved drug available for use or if there is a drug in the approval pipeline that can be used under a compassionate INAD exemption.

Better understanding of the legalities of fish drug use—knowing what drugs are legal for use on fish and how to use them correctly—will help fisheries professionals make better decisions regarding fish health, management, and research. It is imperative for them to know that the FDA can and does monitor fish drug use to ensure compliance with federal law and that it takes considerable time and money to obtain a new drug approval. Fisheries professionals know that therapeutic drug treatments may be the answer in the short term, but if disease problems persist, other solutions that address the root problem (e.g., reducing stocking densities or disinfecting incoming water) will need to be considered.

Understanding the concepts of judicious drug use, that only drugs approved by the FDA or available through a compassionate INAD exemption or other CVM-accepted mechanism can be used, and that it takes a considerable amount of time and expense to gain a new fish drug approval will allow the fisheries profession, particularly fish culturists, to better address demands and constraints now and in the future. It is likely that the role and relevance of hatcheries will continue to grow: now more than ever, hatcheries are needed to produce fish for fisheries enhancement, to propagate imperiled species, and to act as temporary refugia for organisms threatened by anthropogenic and stochastic events. It is likely that an even wider variety of fish species will be cultured in hatcheries in the future. External factors such as climate change may lead to a decline in fish populations, and hatchery-origin fish may be more heavily relied upon to prevent extirpations and extinctions. At the same time that hatcheries face greater operational demands, they may face shrinking budgets. Budget cuts that lead to facility closures will increase pressure on the remaining operations to meet the increasing demand for fish for recreational and commercial fishing and restoration/conservation. Collectively, these factors may contribute to emerging diseases and fish health concerns. The fisheries profession needs to be prepared for these types of scenarios and have a medicine chest that is sufficiently stocked to help maintain the health of hatchery-reared fish. Despite the many misconceptions regarding the use of drugs in fish culture, the use of fish drugs as part of a comprehensive approach to fish health management does not threaten fisheries resources or public safety. It is incumbent on fisheries professionals and the regulatory community to ensure that we maintain this status

and that an adequate number of approved drugs are available in the future to address new and emerging needs in the fisheries fields.

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