Challenges With the Development and Approval of Pharmaceuticals for Fish

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ABSTRACT

With an increase in consumer recognition of the health benefits associated with seafood consumption, the volume of fisheries and aquaculture products consumed by the average American is expected to rise. With a concomitant expectation for high-quality products, aquaculture is likely to become a greater source of consumed fish. As the US aquaculture industry grows, so does the need to provide veterinary services. As with any intensive farming system, appropriate medications are needed to maintain animal health and to manage fish populations. This article introduces some of the challenges associated with drug approvals for aquatic species and describes how the process of development and regulation of drugs for use in aquatic animals differs from that associated with uses in terrestrial species.

KEYWORDS: aquaculture, fish, drug approval, FDA.

INTRODUCTION

Aquaculture can be simply defined as the farming of aquatic organisms. More specifically, aquaculture is the propagation and rearing of aquatic species in controlled or selected environments. Aquatic animals are frequently referred to simply as “fish.” Nevertheless, the term “fish” encompasses a large variety of species including finfish, mollusks, and crustaceans. Just as cattle and swine are different species, each fish is a different species, even similar finfish, mollusks, and crustaceans. Fish of all types can be and are raised for food, or farmed.

Commonly farmed aquatic species within the United States include channel catfish, rainbow trout, Atlantic salmon, hybrid striped bass, tilapia, shrimp, crayfish, and abalone. These species are raised in freshwater and saltwater netpens, open water systems, ponds, raceways, or tanks. Finfish species may be reared to market size (which is typically reached during adulthood) for sale to restaurants, supermarkets, or fish markets. These species include rainbow trout, Atlantic salmon, channel catfish, hybrid striped bass, and tilapia. Alternatively, they may be raised by state and federal

conservation agencies to restock natural populations or to maintain sport fisheries. In these situations, the fish are raised and released as juveniles (or earlier).¹⁻³

Aquaculture is a growing industry in the United States, but production is still only a fraction of that of the cattle, poultry, and swine industries. In 2001, US consumers spent an estimated \$55.3 billion for fisheries products (wild caught). Of the \$55 billion, \$38.2 billion was spent in restaurants and \$276.3 million was spent on fish bought for home consumption. The average per capita consumption of fishery products for 2000-2001 was approximately 15 pounds per year.⁴ By comparison, the corresponding average per capita consumption was 68.4 pounds of poultry products, 116.7 pounds of red meats, 257.1 pounds of eggs, 29.8 pounds of cheese, and 23.2 pounds of milk.⁵

US seafood exports were approximately \$1 billion in 1984; they increased to approximately \$3 billion by 1990 and have remained at about that level since. Yearly expenditures on exports have since remained at about \$3 billion. In contrast, US seafood imports have increased from approximately \$3.75 billion in 1984 to approximately \$10 billion in 2002.⁶

With a concomitant expectation for high-quality products, aquaculture is likely to become a greater source of consumed fish. As the US aquaculture industry grows, so does the need to provide veterinary services. As with any intensive farming system, medications are needed to maintain animal health and manage fish populations. The challenges associated with drug approvals for aquatic species and the differences associated with the development and uses of drugs intended for use in aquatic versus terrestrial species will be explored in this review.

REGULATORY CONSIDERATIONS

In the United States, sponsors of animal drug products obtain marketing approval through the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM). Drug use may be considered illegal if administered to food-producing animals in a manner inconsistent with the FDA-approved product label. The number of drugs approved by the FDA for use in aquatic species is small compared with the number of drugs approved for cattle, swine, or poultry. For this reason, many commonly encountered diseases in fish do not have any FDA-approved treatments. Table 1 provides a list of drugs that are currently approved for use in aquatic species.

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Table 1. Drugs Approved for Use in Aquatic Species*

Drug	Species	Indication
Formalin	Finfish	Control of certain external protozoa and monogenetic trematodes
	Finfish eggs	Control of fungi of the family Saprolegniaceae
	Penaeid shrimp	Control of certain external parasites
Oxytetracycline	Pacific salmon	Marking of skeletal tissue via medicated feed
	Finfish	Marking of skeletal tissue via immersion
	Salmonids	Control of ulcer disease caused by <i>Hemophilus piscium</i> , furunculosis caused by <i>Aeromonas salmonicida</i> , bacterial hemorrhagic septicemia caused by <i>A. liquefaciens</i> and pseudomonas disease.
	Catfish	Control of bacterial hemorrhagic septicemia caused by <i>A. liquefaciens</i> and pseudomonas disease
Sulfadimethoxine/ ormetoprim	Lobster	Control of gaffkemia caused by <i>Aerococcus viridans</i>
	Salmonids	Control of furunculosis caused by <i>Aeromonas salmonicida</i>
	Catfish	Control of enteric septicemia caused by <i>Edwardsiella ictaluri</i>
Sulfamerazine [†]	Rainbow, brook, and brown trout	Control of furunculosis
Tricaine Methanesulfonate	Fish, amphibians, and other poikilotherms	Temporary immobilization as an aid in handling
Chorionic Gonadotropin	Finfish	Spawning aid

*Data from FDA Center for Veterinary Medicine Web site.⁷[†]Not currently marketed.

When animal health is threatened or if suffering or death may result from lack of treatment, the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 provides the legal provisions necessary to allow veterinarians to prescribe products for use in an extralabel manner. Such extralabel uses must adhere to certain restrictions, as follows:

1. A valid veterinarian-client-patient relationship must exist.
2. The drug may not be administered in feed.
3. The use must not result in a drug residue that presents a risk to the public health or is above an established safe level, safe concentration, or tolerance.

Despite the therapeutic options available through AMDUCA, fish culturists have identified many remaining unmet pharmaceutical needs. Many of the products and drugs that have been identified as potentially effective for the treatment of disease in fish are not approved for animals or humans and therefore cannot be prescribed under AMDUCA. Also, the approved antimicrobials are primarily administered as medicated feeds, the extralabel use of which is prohibited. Recently, FDA developed a document to provide guidance to FDA personnel regarding the exercise of regulatory discretion concerning the extralabel use of medicated feeds for minor species. A minor species is any species other than cattle, swine, horses, chickens, turkeys, dogs, and cats. At this time, FDA is unlikely to take regulatory action when medicated feed products approved for use in aquatic species are used in an extralabel manner.⁸ An approved medicated feed

includes not only the drug but also the specific type of feed (eg, salmonid, catfish). While this discretion assists veterinarians and producers, not all fish will consume feeds formulated for other species, and the approved feeds may not meet the nutritional needs of other species. Also, although FDA may not take action, the guidance does not make extralabel use legal and the guidance may be withdrawn at any time.

The needed medications include those to treat coldwater disease, columnaris and sea lice in salmonids, improved treatments for the fungus *Saprolegnia* on eggs and fish, additional medications to treat enteric septicemia and columnaris in catfish, and additional anesthetics and spawning aids. Coldwater disease, caused by the bacteria *Flavobacterium psychrophilum*, and columnaris disease, caused by the bacteria *Flexibacter columnare*, can cause external skin lesions and systemic infections in freshwater fish.⁹⁻¹¹ The organism that causes columnaris can also be associated, along with other bacterial organisms, with infections of the gills.⁹⁻¹¹ Enteric septicemia is a systemic infection, primarily of catfish, caused by the bacteria *Edwardsiella ictaluri*.^{9,11} This disease can cause high mortality and occurs primarily during the late spring to early summer and fall when water temperatures are between 18°C and 28°C.^{9,11} *Saprolegnia* spp fungi can infect the external surface of fish and eggs. On eggs, the fungus infects eggs that have died prior to hatching.¹⁰ When *Saprolegnia* is present in large enough quantities on eggs, the fungus can spread to the healthy, unhatched eggs, causing loss of all the eggs. On fish, the fungus can infect any skin wound that may occur after handling fish to transfer them

among tanks or wounds that are secondary to some other skin infection.¹⁰ The infection then can increase in severity such that it extends through the skin of the fish and into the underlying muscle. An effect of external (skin) infections is the disruption of the skin, which if severe enough, can disrupt osmoregulation to such an extent that death results.⁹⁻¹² Sea lice, *Lepeophtheirus salmonis* and *Caligus elongatus*, being the primary species of concern in North America, are external parasites of marine salmonids, both wild and farm-raised. Susceptible fish species, including Atlantic salmon and Arctic char, are not infested until they are placed into marine environments such as marine netpens. The lice cause excoriations on the skin of the fish when feeding. Infestation with large numbers of lice on farm-raised fish, as well as rubbing on the nets of the pens because of the lice, can cause severe excoriation and ulceration.¹²⁻¹⁴

Unfortunately, significant economic burdens frustrate attempts to address these unmet needs. Under the best of circumstances, the financial investment required to obtain an approval of a New Animal Drug Application (NADA) is substantial. A new animal drug approval can cost over \$40 million.¹⁵ These expenditures reflect the costs associated with the statutory requirements that each NADA contain the data needed to confirm that the product is safe (both for the target animal species and for human consumption), will not pose environmental concerns, and is effective for the stated indication. 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 to \$8 million.¹⁶ The requirements associated with a NADA for an aquatic species are the same as those required for an approval in any other animal species. However, because of the small size of the current US aquaculture industry, the economic return on those drugs may not be great enough to justify the investment.

At this time, investigational new animal drug application (INAD) exemptions exist that permit compassionate use of drugs for aquatic species while data are generated for approvals. The compassionate use program allows fish culturists, many of whom are state and federal hatcheries 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 participants are part of collaborative efforts to generate the data needed for a NADA. The drug uses and results of all trials are reported to CVM to help complete the animal safety and effectiveness components of a NADA. While compassionate use data are not generally generated under controlled study conditions, and therefore cannot provide all the information needed to support an approval, this information can provide important supplemental information to confirm that the product is safe when administered in therapeutic doses.

Examples of the types of studies required for US approval of drug products for use in aquatic species are described below.

Animal Safety

Safety studies must be conducted according to Good Laboratory Practices, as defined in the Code of Federal Regulations Title 21 (21 CFR), Part 58.¹⁷ While ideally, a compound is tested in every animal species for which it is intended, requiring studies for every species of fish potentially treated with that compound would be economically prohibitive. The current size of the aquaculture market would not provide an adequate return on investment if hundreds of studies were required for each approved drug or disease claim. Therefore, the species included in studies, one of which generally constitutes a large proportion of the species to which the drug will be administered when approved, are often considered to be a representative of all other related fish species. However, such extrapolation must be considered with caution because of the number of variables that can influence compound toxicity in aquatic species.

Water temperatures can affect the metabolism and excretion of a given drug, thereby affecting tissue drug residues as well as the animal safety and effectiveness for disease treatment.¹⁸ As water temperature varies, so does fish metabolism and, consequently, drug pharmacokinetics. Because of the small amount of information about the effects of temperature on pharmacokinetics and pharmacodynamics, drugs are evaluated at different temperatures to detect any changes that may occur. Altered drug toxicity and resulting fish mortality can occur (even at recommended doses) with changes in water temperatures, pH, hardness, oxygen levels, or organic matter concentrations.¹⁹ Some drugs are associated with increasing toxicity as water temperatures increase.^{18,19} However, it is impractical to test every species at every water temperature likely within a particular aquatic environment. This is particularly true for immersion treatment, where fish can be exposed to varying water conditions across a range of geographic regions.

An additional complication is that the diseases for which treatments are administered are often associated with gill pathology. The gill is frequently the organ exhibiting a toxic response. Therefore, even with high-quality data in representative fish species, a certain amount of uncertainty regarding the animal safety of the compound cannot be avoided.

When dealing with fish, a compound's safety cannot be assumed, even if it is considered very safe for use in mammals. For example, ivermectin is a widely used drug with a wide margin of safety in cattle, sheep, goats, swine, rabbits, cats, and dogs. While ivermectin would be useful to treat external parasites (sea lice) in Atlantic salmon, this compound is associated with a narrow therapeutic margin in this species.²⁰

Effectiveness

Generally, field studies conducted to demonstrate drug effectiveness for a NADA should closely mimic the actual conditions of use. However, attempting to conduct field studies at aquatic production facilities poses a logistic dilemma. To reduce animal numbers to a manageable size, the studies can be conducted on a smaller scale, while maintaining conditions similar to those found at the production facility. However, even with this compromise, small ponds (0.25 acres) or small tanks (700 gallons), with fish densities similar to those at industry production level, may contain several hundred to several thousand fish. This makes the collection of clinical data, such as mortality, feed consumption, or changes in fish behavior, difficult to capture. With warm water temperatures, dead fish may degrade quickly or sink to the bottom of a murky pond before being counted or collected. Catfish in a typical pond are frequently not visible except at feeding. For fish reared in clear water, such as trout or salmon raised in netpens with underwater cameras, the collection of some types of data may be easier owing to improved visibility. However, studies involving offshore netpens necessitate the collection of data on pontoons located alongside the netpens. Under these conditions, the collection of data is highly dependent on weather conditions.

Antimicrobials that are approved for use in other food-producing species are commonly investigated for use in fish. This is because an approved drug product that can be administered to fish often is available. Since certain types of data can be used for approvals in multiple species, specifically some of the human food safety data, the cost of adding an indication to an approved product for use in aquatic species is thereby reduced. However, when compared with mammals, fish have some definite differences in pharmacokinetics that need to be considered. For example, differences in bioavailability of tetracycline, quinolones, and beta-lactam antimicrobials have been documented. Oxytetracycline and amoxicillin are not well absorbed from the intestines of fish. The doses of these antimicrobials are generally 2 to 5 times that needed to produce therapeutic systemic concentrations in mammalian species.¹⁹ The bioavailability of oxytetracycline in rainbow trout in fresh water may be as low as 8% and as low as 2% in Atlantic salmon living in seawater. Trimethoprim and ormetoprim are almost completely absorbed from the fish intestine and have a high volume of distribution, but the systemic availability of sulphonamides in Atlantic salmon in seawater is less than 40%. For several antimicrobials, the cations present in seawater consumed for osmoregulation and in feeds inhibit the absorption of antimicrobials from the intestine. Tetracyclines and quinolones chelate with di- and trivalent cations with the level of binding varying among the drugs in each antimicrobial class. Serum concentrations of oxolinic acid and difloxacin were found to be 2 to 5 times higher in fish held in fresh water than for fish held in salt water.¹⁹

Drug excretion is also affected by the water type. Oxolinic acid was found to be excreted about 6 times faster in rainbow trout held in salt water compared with those held in fresh water. Consequently, this drug has the potential to be effective in fresh water at 1 dose, but because of rapid excretion, ineffective at the same dose against the same pathogen in the same species when administered to fish held in salt water. The pharmacokinetics of quinolones is affected by water temperature as well. However, water chemistry has a larger effect. Tetracyclines are slowly excreted in the fish with the elimination half-life increasing with decreasing water temperature.¹⁹

While much is known about pathogens and their clinical effect in the major animal species (ie, cattle, swine, and poultry), the same is not true for many diseases in fish. Some pathogens have not been classified, such as the pathogen associated with epitheliocystis, a gill disease caused by a chlamydia-like organism. The clinical significance of this pathogen is variable, with a 6% to 75% prevalence and a 4% to 100% mortality rate associated with infection. The prevalence is noted to be higher in cultured fish, indicating that the disease may become a concern to fish health professionals and culturists.^{21,22} The histopathology and pathogenesis of *Edwardsiella tarda* (which causes Edwardsiellosis in channel catfish and in other warm-water finfish species) was only recently described.²³ The economic impact of this disease may become more significant if husbandry conditions change from the earthen ponds (in which catfish are usually reared) to tanks (where the disease is more prevalent).

Reproductive hormones, rather than being used to treat disease or to alter growth rate, are used as a component of population management to manipulate gender. Hormones may be used to induce egg or milt production. Human chorionic gonadotropin, luteinizing hormone releasing hormone and its analogs, and carp pituitary have been used to induce spawning in various species of fish. The specific endogenous reproductive hormones and the effects of these hormones on sex determination, sperm development, and egg development and release have not been described for all fish species. Human chorionic gonadotropin, which is approved for use in finfish, induces spawning in some species but has no effect in others. In some species, luteinizing hormone releasing hormone or its analog will induce spawning. Some species require one drug to induce egg maturation and a different drug to induce egg release. Others require dopamine inhibition in conjunction with a releasing hormone to induce the release of gonadotropins and the subsequent initiation of spawning behavior.²⁴ Drugs to induce spawning are very important for conservation programs since many fish will not spawn naturally in captivity. These drugs are also important when creating hybrids of species that do not spawn naturally.

Various forms of estrogen and testosterone have been used to manipulate the sex of either broodstock fish or the fish that will

be available to consumers. These drugs must be administered at the correct dose for the appropriate length of time in early life-stages of these fish (the time of sex differentiation). The reason to reverse fish gender varies among species. There is a very specific relationship between drug dose, sexual outcome, and the finfish species. Since a drug and dosage regimen that has desirable effects in one finfish species can have undesirable effects in a different species, separate effectiveness studies are needed to support each production claim. With tilapia, fish reach reproductive maturity before reaching market size. Fish that are spawning have poor feed conversion, expending energy on reproduction rather than growing. Also, male tilapia tend to be larger than females, consequently, an all male population is preferred. In contrast, rainbow trout producers prefer to raise all female populations since males reach sexual maturity prior to achieving the preferred market size. Such early maturation is undesirable because sexual maturity in rainbow trout is associated both with reduced disease resistance and with reduced flesh quality. Currently, no drugs are approved for use for gender manipulation of fish.²⁵⁻³¹

Manufacturing Concerns

Because of current husbandry practices, medicated feeds are one of the most practical methods to administer oral drugs to fish. The challenge facing manufacturers of these medicated feeds is that a single premix formulation may be incorporated into or mixed with multiple types of feed. From a regulatory perspective, each feed type is considered a different drug product and therefore requires separate studies to support its approval. For example, catfish feed is grain based and is produced as a floating feed. Salmonid feeds sink and contain animal-based protein and fat. Thus, not only are the ingredients different, but these varied formulations are manufactured using different processes. Moreover, the different feed components may affect the accuracy of the analytical methods used during product quality assurance test procedures. A different analytical method may be needed for each type of feed, even if the active ingredient remains unchanged.

Animal drugs must be manufactured to have and maintain the necessary quality, strength, purity, and identity. Quality cannot be inspected or tested into a finished product. Each step of the manufacturing process must be controlled to provide assurance that the finished product will be acceptable. For these reasons, approved drugs must be manufactured according to current Good Manufacturing Practices (cGMP), as defined in 21 CFR Parts s 210, 211, 225, and 226.¹⁷ Some of the drugs being evaluated for aquatic species are actually chemicals used in the aquaculture industry or in other industries. The companies may not produce the chemicals according to cGMP. These chemicals are attractive to fish culturists and to those assembling data for approvals because some of these chemicals are already used at aquaculture facilities to

maintain water quality and have US Environmental Protection Agency (EPA) registration. Alternatively, they may have been used in water treatment facilities or health and cosmetic products for people, indicating that studies have already been completed to assess safety issues pertaining to human safety/environmental toxicology. Sometimes these same studies can be used as part of a NADA.

Environmental Concerns

Currently the law provides exceptions for preparing an environmental assessment or environmental impact statement for some drug approvals. These exceptions are included in 21 CFR Part 25.¹⁷ Two types of these instances are animal drugs intended for use in nonfood animals and under prescription or a veterinarian's order, or therapeutic use in terrestrial species.

Regardless of the method used to administer drugs to fish, the environmental impact of that use must be considered. With medicated feeds, environmental exposures may occur through incomplete feed consumption or by the excretion of biologically active metabolites. The environmental fate of the drug and metabolites in the environment varies.

When compounds are administered in medicated feeds, wild fish living near aquaculture facilities may experience unintentional drug exposure. Some aquaculture facilities have earthen ponds or recirculating water systems that reduce environmental exposure (as compared with open-water netpens). However, others do not. Therefore, under the National Pollutant Discharge Elimination System (NPDES), regulations were instituted to regulate the allowable discharge from aquaculture facilities. The facilities are required to obtain permits that allow for the discharge of specified amounts of certain chemicals.

Because of concerns that the NPDES permits were inconsistent and potentially inadequate, EPA published a Notice of Proposed Effluent Guidelines Plans including fish hatcheries and farms as candidate industries for effluent guidelines rule-making projects in 1998. The guidelines would regulate industrial discharges to surface water and publicly owned treatment works. In 2000, EPA announced its intent to help reduce nutrient loading from commercial agricultural and from industrial operations. Their proposal was to develop national effluent limitation guidelines and standards for commercial and public aquaculture operations.³² In September 2002, the proposed rule for Effluent Limitations Guidelines and New Source Performance Standards for the Concentrated Aquatic Animal Production Point Source Category was made publicly available for comment, proposing a new technology-based effluent limitations guideline and standards for wastewater discharges (including nutrients) associated with the operation of new and existing concentrated aquatic animal production facilities.³³ The comment period closed on

December 11, 2002. On December 29, 2003, a summary of the data received since the original proposal and a description of how EPA may use the data to address comments and develop a final rule were made publicly available for comment. The comment period closed on February 12, 2004.

PHYSIOLOGICAL CHALLENGES THAT IMPACT DRUG METABOLISM AND USE IN FISH

Some fish species have both freshwater and saltwater phases of their life cycles. These species are referred to as diadromous. Diadromous fish are subdivided into those species that are anadromous and those that are catadromous. Anadromous species, such as striped bass, Atlantic salmon, shortnose sturgeon, steelhead trout, and American shad, to name a few, spend most of their adult life in salt water but spawn in freshwater lakes or rivers. Catadromous fish, such as the American eel, spend most of their adult life in fresh water and migrate to salt water to spawn.³⁴

Salmonids can be used as an example of the kinds of physiological changes that can occur across the life-stages of these fish. Juvenile salmonids undergo smoltification, which is the transformation from the freshwater parr to the saltwater smolt stage. Photoperiod and water temperature changes, each contributing to differing degrees depending on the salmonid species, induce this transformation. Early life-stage salmonids are generally reared in hatcheries until smoltification occurs, at which time the fish are transferred to sea netpens. Depending on the salmonid species, smoltification occurs at ages of less than 1 month up to 3 years of age. The transformation involves both morphological and physiological changes. The major change is in the regulation of salt and water balance. Salmonids' osmotic concentration in body fluids is about one third that of sea water, whether in fresh water or salt water. To adapt to a saltwater environment, the gills, kidney, and urinary bladder undergo changes to perform functions opposite those present during the freshwater stage. In fresh water, the gill chloride cells take up ions from the water. Ions are also reabsorbed back into the blood through the wall of the bladder. In salt water, the gill chloride cells actively secrete salts absorbed from consumed water. The kidney retains consumed water and the urinary bladder ceases reabsorbing ions. The smoltification stage is a stage that can be associated with a greater need for disease treatment for cultured anadromous salmonid species. Thyroid and growth hormone secretion increases, and the fish maintain a sustained growth rate (as compared with the seasonal fluctuations commonly seen in freshwater species). The increase in cortisol secretion initiates the differentiation of the gill chloride cells, which results in an increase in the level of sodium and potassium-adenosine triphosphatase, and a reduction in body lipid content. However, this increase in cortisol levels also produces an immunosuppression that renders fish more susceptible to disease.³⁵

The various physiological changes, as well as the environmental changes, can alter drug metabolism and excretion, as described previously. Pathogens and parasites affecting the fish may also differ across water conditions (eg, sea lice in Atlantic salmon, which are a problem only when the fish are placed in seawater netpens). Because of the physiological differences between saltwater and freshwater fish, the safety and effectiveness of drugs cannot be assumed similar, either between anadromous and catadromous species or between life-stages within a diadromous species.

DRUG ADMINISTRATION/DOSING CHALLENGES

The most practical way to deliver many medications to groups of fish is through feed. However, medicated feeds present challenges with administration and environmental exposure. When an individual animal is treated with an injectable drug, one can be sure that the animal receives the required dose. With medicated feeds, differences in appetite due to disease, feeding hierarchies, and water temperature can affect the amount of drug reaching each fish. While culturists and animal health care providers can adjust the concentration of medication in the feed to compensate for changes in the average feeding rate, most health care providers assume that within any population, some fish will be overdosed and some will be underdosed. A tank in a trout hatchery can contain thousands of fish. Production level catfish ponds generally cover 10 to 20 acres of surface area, have a depth of 3 to 6 feet, and are stocked with a mixed life-stage population at a rate of 5000 to greater than 10 000 fish per acre.³⁶ Consequently, the healthiest, most aggressive fish will receive an adequate amount of drug when administered as a medicated feed, while the smaller or diseased animal will not likely receive sufficient medication.

Even when drug administration for aquatic species seems simple, the opposite is often true. Small fish, which may weigh only a few grams, and large groups of fish can be treated by immersion in a drug solution or treated orally with a medicated feed. However, very early life-stage fish may not yet be consuming feed since they have a yolk sac from which they obtain needed nutrition. This then limits the method of treatment to immersion. However, culturists are often confronted with the problem that the size and type of the containment method prohibits the use of immersion therapies. To administer an immersion treatment to a seawater netpen, divers must be used to surround the netpen with a tarp. Weather conditions can also significantly impact the time when the immersion treatments are administered. Moreover, if immersion treatments are added to ponds or systems with low water exchange rates, the product must degrade quickly or be quite safe since once the medication is added to the water, removal or dilution is unlikely to occur. Drug delivered via injection is difficult to administer, physically

impractical, and time consuming and may be excessively stressful to the fish. The use of such products is generally limited to the larger and individually valuable fish, such as broodstock.

Sometimes, the same pathogen may present as an external or systemic disease, each being treated by different routes of administration or with different drugs. *F. columnare* can present as a systemic infection, an external infection affecting the skin and gills, or as a component of bacterial gill disease.⁹⁻¹¹ The same drug may be used to treat both infections, with an immersion treatment being more effective for the external infection and a medicated feed being more effective for a systemic infection. Or different drugs with different routes of administration may be needed to treat the systemic and external infections. If fish are sufficiently small, an immersion treatment may be adequate to treat a systemic infection or may be the only practical form of treatment.

Rather than thinking of treating individual animals for a disease, most disease claims for aquatic products are for population management and control of mortality. The goal of treatment is to control the progression and spread of the pathogen or parasite within the population and limit morbidity and mortality while maintaining normal growth and development. The size of production facilities, the size and density of the fish, and the inability to identify individual fish all have an impact on how medications are administered and how studies are designed to evaluate drug effectiveness.

INITIATIVES TO INCREASE THE NUMBER OF APPROVED AQUACULTURE DRUG PRODUCTS

To encourage the development of products for use in aquatic species, a cooperative effort was formed to assist with these drug approvals. The National Aquaculture Act of 1980 and the National Aquaculture Improvement Act of 1985 provided legislation for the development of aquaculture in the United States and the formation of the Joint Subcommittee on Aquaculture (JSA). The JSA is a federal interagency committee tasked with coordinating and disseminating aquaculture information of national and international interest. The JSA recognized that the approval of safe and effective drugs is necessary for the health management of aquatic species, as well as for the production of a high-quality, safe, and wholesome consumer product.³²

In 1990, JSA members formed the Quality Assurance in Aquaculture Production Working Group. This group's mission is to increase understanding of, and compliance with, federal requirements regarding drugs, chemicals, and biologics used in aquaculture production in the United States through education and coordination of efforts of government, industry, and academia.³² Cooperative efforts formed in 1995 between federal agencies such as the US Fish and Wildlife

Service, the US Department of Agriculture (USDA), and the US Geological Survey, and other private and public partners were intended to facilitate generation of the animal safety and effectiveness, food safety, and environmental safety information required for product approvals. This cooperative effort became the International Association of Fish and Wildlife Agencies Federal State Aquaculture Approval Partnership Project.³²

For most products intended for use in minor species, there is a mismatch between the potential return associated with the marketing of these products and the investment needed to meet the requirements of a NADA. For this reason, a novel cooperative effort was created to generate the data needed to support the approval of indications for minor species and minor uses. Minor species include, but are not limited to, sheep, goats, ratites, game birds, honeybees, bison, deer, and fish. Minor use drugs are those used for diseases that occur infrequently within limited geographic regions. In 1982, the USDA and the FDA established a national program to address the shortage of drugs for minor uses and minor species of agricultural or economic importance. In 1993 this program became the National Research Support Project Number 7 (NRSP-7) Minor Use Animal Drug Program.¹⁶

CVM has a full-time position for a liaison between the NRSP-7 program, investigators, pharmaceutical firms, and CVM for all minor species/minor use concerns. The NRSP-7 program provides funding and oversees studies addressing the effectiveness, animal safety, human food safety, and environmental safety sections of a NADA.¹⁶ However, funding challenges continue to exist, discouraging the product development needed to address unmet therapeutic needs.

To address this problem, a coalition was formed in 1999 and included producer commodity groups, pharmaceutical companies, veterinarians and others with an interest in seeing more drugs available for minor uses and minor species (MUMS). The MUMS Coalition drafted legislation for introduction to Congress. The Minor Use and Minor Species Animal Health Act, enacted in August 2004 (Public Law 108-282), amends the Federal Food, Drug, and Cosmetic Act (the Act) with regard to new animal drugs for minor uses and minor species. The MUMS Animal Health Act changes the Act in three major ways. The first is conditional approval of drugs which allows marketing of the drug before all the necessary effectiveness data is collected. The second is the indexing of drugs for nonfood animals that are unlikely to be approved because the potential market is too small for the financial return to support the approval process. The third change provides for drugs to be designated as for a minor use or minor species. Companies with designated drugs that are subsequently approved will receive 7 years of marketing exclusivity for that drug rather than the 5 years of marketing exclusivity currently available under the Act. Grants to sup-

port the development of safety and effectiveness data for designated drugs will also be available. An Office of Minor Use and Minor Species Animal Drugs Development will be established at CVM.¹⁶

While pharmaceutical companies have regulatory affairs departments to guide companies through the approval process, this guidance was absent in the newly formed aquaculture partnerships. To provide some of the organizational needs, the position of National Aquaculture New Animal Drug Application Coordinator was created. While the CVM NRSP-7 liaison works with all minor species and minor uses, the National Aquaculture NADA Coordinator is specifically designated to attend to issues associated with products intended for aquaculture uses. The National Aquaculture NADA Coordinator not only guides the development of NADA packages but also acts as a liaison between those individuals generating the data, the pharmaceutical firms that may use the data as part of their approval package, and CVM.³²

Because it is impractical to require safety (animal and human food safety) and effectiveness studies for each aquatic species for which a drug may be intended, the grouping of aquatic species into "crop groups" based upon physiological and husbandry conditions is an active area of research. Grouping based on variables such as habitat conditions and drug metabolism is currently under investigation. If such a grouping is successful, 1 aquatic species may serve as a representative in the confirmation of safety (animal safety and/or human food safety), effectiveness, or both, for a particular group of fish.

Currently, research is being conducted in an attempt to group fish to reduce the number of studies needed to establish food safety and animal safety and effectiveness. Because of the large number of aquatic species, testing drugs on each of the species is impractical. Therefore, efforts are under way to explore the use of pharmacokinetic information to determine and demonstrate the manner by which certain species may be grouped. These efforts are occurring largely under the direction of Dr Renate Reimschuessel at FDA-CVM's Office of Research, and Dr John Babish of Cornell University and the US Geological Survey's Upper Midwest Environmental Sciences Center (UMESC). The objectives of Dr Reimschuessel's research are to identify a rationale to group aquatic species (finfish) for human food safety, to conduct metabolism and residue depletion studies of selected drugs in a variety of fish, and to identify species with similar metabolic profiles and residue depletion patterns. The end result may be a single model fish species, with the slowest depletion, which can be used to establish the withdrawal time needed to ensure that the product is safe for human consumption. The withdrawal time would be applicable to multiple fish species for one or more drugs.³⁷

Although the work of Dr Reimschuessel has focused primarily on human food safety, samples have also been collected to pro-

vide basic pharmacokinetic information to support an extrapolation of target animal safety and effectiveness across species within a group. This project is in its early stages and the outcome cannot be predicted. The pharmacokinetic information may be useful as bridging studies to add additional species to an approved drug claim. Drugs currently under investigation include albendazole, a benzimidazole anthelmintic; ivermectin, an avermectin antiparasitic; and flumequin, a quinolone antimicrobial. The species included in the project are rainbow trout, tilapia, channel catfish, yellow perch, Atlantic salmon, hybrid striped bass, and large mouth bass. Dr Babish's research focuses on characterizing species-specific drug metabolism, with an emphasis on the cytochrome (CYP) P450 enzyme system. The species included in this project are rainbow trout, tilapia, walleye, yellow perch, summer flounder, hybrid striped bass, and channel catfish.³⁷

Investigators at the UMESC have also been conducting grouping studies. Their plan includes developing a database that would be sensitive enough to identify differences and similarities between groups. Fish would be grouped by temperature, activity level, and phylogenic classification. Species representing primitive and more advanced species would also be included in investigations.³⁸ Under this plan the pharmacokinetics of benzocaine have been investigated in rainbow trout held in different water temperatures. The benzocaine accumulation in the fillet tissue was similar at the temperatures tested.¹⁸

Ultimately, investigators may find that fish will be grouped differently for food safety, target animal safety, and effectiveness. For example, while human food safety may be based on drug metabolism and water temperature, effectiveness may be based on rearing conditions and disease occurrence, and target animal safety may best be based on toxicological response and drug metabolism. Environmental safety may best be reflected by similarities in husbandry conditions. While it will always be important to acknowledge the limitations associated with the absence of specific information for each of the hundreds of species, crop grouping has the potential to reduce the costs associated with drug approvals, while increasing the number of approved drugs for a large number of fish species.

CONCLUSION

Federal and state conservation agencies are highly motivated to help with the approval process of drugs for aquatic species because they would like to see safe and effective drugs that can be used for disease management and, because in some localities, drug use is limited by state or federal law to only those products previously approved by the FDA or USDA. The resulting partnerships and coalitions will help to ensure that such approvals are obtained. Much valuable research has been done, but much remains to be done.

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