FARAD Digest

Current approved drugs for aquatic species

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Aquaculture is an important developing international industry. Approved pharmaceutical agents available to veterinarians in the United States are limited in their therapeutic scope and efficacy. Ensuring preharvest food safety and preventing illegal drug residues are extremely important issues in the selection of therapeutic regimens for aquatic species. Currently available therapeutic substances used in aquaculture can be classified as FDA-approved drugs, FDA-unapproved **low-regulatory-priority treatments (LRPTs)**, **Environmental Protection Agency (EPA)**-registered products (eg, algaecides, herbicides, and fish toxicants), USDA-licensed biologics (eg, bacterins and diagnostics), and feeds (eg, glycans and probiotics).[1,2] As for other food-producing species, extralabel use of drugs in feed formulations is illegal.[3] However, a recent compliance policy guideline[3] outlines criteria by which veterinarians may use extralabel treatments in the feed of minor species on a limited basis. This Food Animal Residue Avoidance Databank Digest reviews drugs currently approved for use in aquatic species **(Appendix 1)**,[1,4-9] chemicals that are not approved but are considered by the FDA's **Center for Veterinary Medicine (CVM)** to be of low regulatory priority **(Appendix 2)**,[2] and policies that can affect the use of these products.[5]

Low-Regulatory-Priority Drugs

A number of substances commonly used in the treatment of diseases and production enhancement[1,2] in aquatic species have not been approved by the FDA (Appendix 2). Technically, these compounds cannot be administered in a manner that is in compliance with the **Animal Medicinal Drug Use Clarification Act's (AMDUCA's)** definition of extralabel drug use. The FDA has reviewed the use of a number of compounds and has classified them as new animal drugs of low priority. It is unlikely that the FDA will object to use of these substances if the following criteria are met[2] (Appendix 2):

- The substances are used for specific indications, species, and life stage(s).
- The substances are used according to good management practices.
- The product is of an appropriate food or medical grade for the use in food-producing animals.
- The substance is used at prescribed dosages.
- Adverse effects on the environment must be negligible.

The FDA has reserved the right to consider these drugs and products as unacceptable for use in food-producing animals in the future. The FDA's enforcement position on the use of LRPT should not be misconstrued as an approval or support of safety or effectiveness. These substances must comply with the EPA's National Pollutant Discharge Elimination System requirements. Facilities and veterinarians are not exempt from complying with other federal, state, and local environmental laws and regulations.[a]

Clove Oil and Eugenol for Anesthesia of Fish

Despite the availability of approved products, clove oil (with its active components eugenol, isoeugenol, and methyleugenol) is being used as an anesthetic agent for fish.[10] Food safety concerns, including evidence for carcinogenesis in laboratory animals, have prompted the CVM to issue a compliance document on the use of clove oil in aquaculture.[10] Neither clove oil nor its components may be used in food animals (including fish) that could be consumed by humans.

Extralabel Drug Use Policy

Section 530.11 of the AMDUCA specifically prohibits the "extralabel use of an approved new animal drug or human drug in or on an animal feed."[3] The FDA has determined that for some minor species (farmed fish and birds) for which there are few approved drugs, the only practical method of delivery is in the feed. For those situations, the FDA's CVM has adapted a new **Compliance Policy Guide (CPG)** for the extralabel use of medicaments in feed. This CPG does not make the practice of extralabel drug administration in feed legal, but rather the FDA will "not ordinarily consider regulatory action" if certain conditions are met.[3] The medicated feed is used in an extralabel manner only for treatment of minor species as defined in the Code of Federal Regulations (21 CFR 514.1 (d)(1)(ii)). In an aquatic species, the extralabel use of medications added to feed is limited to products approved for use in other aquatic species. Additionally, it is essential that a valid veterinarian-client-patient relationship exists. All the usual record keeping and extended withdrawal requirements apply. As was true before AMDUCA and now, if a residue occurs, any liability would rest with the practitioner and producer. A veterinarian choosing to violate the Food Drug and Cosmetic Act under this policy should carefully review the CPG and consider the amount of liability he or she is willing to accept.

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EPA-Approved Aquaculture Products

In addition to FDA-reviewed drugs, there are a number of products registered by the EPA, including algaecides, herbicides, and fish toxicants. It is illegal to use products registered by the EPA in an extralabel manner. Before purchasing or using any of these commercial products, practitioners should carefully read the label to make certain that the product is approved for its intended use.[1]

[a]Effluent Guidelines, US Environmental Protection Agency, Washington DC. Available at: www.epa.gov/guide/aquaculture/. Accessed Apr 25, 2003.

References

1. *Guide to drug, vaccine and pesticide use in aquaculture*. Beltsville, Md: National Agriculture Library, USDA, 1994.

2. Low regulatory priority aquaculture drugs. Available at: www.fda.gov/cvm/index/aquaculture/LRPDrugs.pdf. Accessed Apr 25, 2003.

3. Extra-label use of medicated feeds for minor species. Compliance policy guide. Office of Regulatory Affairs. United States FDA. Available at: www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg615-115.html. Accessed Apr 25, 2003.

4. United States FDA. Oxytetracycline hydrochloride for marking fish; availability of data. *Fed Regist* 2002;67:46527–46528.

5. United States FDA. Aquaculture drugs (a chemical hazard). In: *Fish and fishery products hazards and controls guidance*. 3rd ed. Washington, DC: US FDA, Center for Food Safety and Applied Nutrition, Office of Seafood, 2001;127–144.

6. Formalin solution. Title 21, part 529, section 1030. In: *Code of federal regulations*. Washington, DC: US Government Printing Office, 1999; 21 CFR 529.1030.

7. Tricaine methanesulfonate. Title 21, part 529, section 2503. In: *Code of federal regulations*. Washington, DC: US Government Printing Office, 1999;21 CFR 529.2503.

8. Oxytetracycline. Title 21, part 556, subpart B, section 500. In: *Code of federal regulations*. Washington, DC: US Government Printing Office, 1999;21 CFR 556.500.

9. Sulfadimethoxine. Title 21, part 556, subpart B, section 600. *Code of federal regulations*. Washington, DC: US Government Printing Office, 1999;21 CFR 556.600.

10. United States FDA. Guidance for industry: status of clove oil and eugenol for anesthesia of fish. Available at: www.fda.gov/cvm/guidance/guide150.doc. Accessed Apr 25, 2003.

Appendix 1

Food and Drug Administration-approved aquaculture new animal drugs

Generic product name	Product/NADA	Species	WDT
Chorionic gonadotropin	Chorulon/140-927	Fin fish	Not for use in food-producing fish
Formalin	Formalin-F/137/687 Paracide-F/140-831 Parasite-S140-989	Salmon, trout, bluegill, catfish, largemouth bass	WDT not specified
Tricaine methane sulfonate (MS-222)	Finquel/42-427 Tricaine-S/200-226	Fish and other cold-blooded animals	21-d WDT
Oxytetracycline hydrochloride	Terramycin/038-439	Salmon, catfish, lobster	Salmon: 250 mg/kg/d (113.6 mg/lb/d), 7-d WDT; or 2.5–3.75 g/d for 10 d, 21-d WDT Catfish: 21-d WDT Lobster: 50 mg/kg/d (22.7 mg/lb/d) for 5 d; 30-d WDT
Sulfadimethoxine and ormetoprim	Romet 30/125-933	Salmonids, catfish	Salmonids: 42-d WDT Catfish: 3-d WDT
Sulfamerizine (not currently available)	Sulfamerazine in fish grade/033-950	Rainbow, brook, and brown trout	21-d WDT
Nifurpirinol	Furanace/099-568	Not for use in food-producing fish/ approval for aquarium species only	

WDT= Withdrawal time. NADA = New animal drug application.

Appendix 2

Nonapproved drugs of low regulatory priority

Product name	Dose	Species	Indication(s)
Acetic acid	Dip 1,000–2,000 mg/L	Fish	Parasiticide
Calcium chloride			Egg hardening
Carbon dioxide gas		Warm, cool, and cold-water fish	Anesthetic
Fuller's earth		Fish	Reduce adhesiveness of eggs
Garlic		Salmonids	Helminthes and sea lice
Hydrogen peroxide	250–500 mg/L	All life stages of fish	Fungi control
Ice			Transport: reduce metabolic rate
Magnesium sulfate	30,000 mg/L	All life stages of fish	External crustacean infections and monogenetic trematodes
Onion		All life stages of fish	External crustaceans and sea lice
Papain	0.2% solution	Fish	Improve hatchability of eggs
Potassium chloride		Fish	Relieve stress/prevent shock
Povidine/iodine compounds	50 mg/L for 30 min		Egg disinfectant
Sodium bicarbonate	142–642 mg/L for 5 min	Fish	Anesthesia
Sodium chloride	1%–2% solution	Fish	Relieve stress and prevent shock
Sodium sulfite	15% solution for 5–8 min	Fish	Improve hatchability of eggs
Tannic acid		Fish	Denature egg adhesives
Thiamine hydrochloride		Salmonids	Thiamine deficiency
Urea		Fish	Denature egg adhesives