



HFA-305

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 31 2003

Professor John Haas Carter, III
Goucher College
1021 Dulaney Valley Road
Baltimore, Maryland 20214

Re: Citizen Petition #93P-0396

Dear Mr. Carter:

This is a final response to Citizen Petition #93P-0396, submitted by you on behalf of the Committee on Safe and Effective Aquarium Drugs (COSEAD) concerning new animal drug applications (NADA's) for current and future products marketed for the diagnosis, control, and treatment of diseases in freshwater and marine aquariums. The petition was filed with the Food and Drug Administration (FDA, agency) on October 19, 1993.

The citizen petition, filed with FDA pursuant to the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. §§ 321 et seq.) asks FDA to:

- (1) impound aquarium fish drugs sold without drug approval and enjoin manufacturers and distributors from further manufacture and distribution pending approval;
- (2) require complete NADA's for all current and future products marketed for the diagnosis, control, and treatment of disease in aquariums, with such applications to include: (a) data on efficacy by species including the probability of recovery and whether the recovered animal will be suitable for breeding, (b) statements indicating those species for which a product is safe and those for which it is unsafe, (c) data on the impact of the nitrogen cycle in fresh and salt water aquariums and details on the effects on ammonia and nitrate levels, and (d) similar data for all recommended combination uses;
- (3) require fish drugs be made with consistent purity and potency and that they be manufactured in compliance with then current good manufacturing practices (CGMP's) under 21 CFR 514.1(b)(5);
- (4) require adequate labeling of aquarium drugs that would include ingredient listing and new animal drug approval numbers;
- (5)(a) require aquarium fish products containing toxic ingredients, antibiotics, or known or suspected carcinogens to: (i) carry conspicuous warnings of risks to the consumer and

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the environment, (ii) instructions for product disposal, and (iii) child-resistant packaging; and (b) prohibit the sale to minors of aquarium fish products containing toxic ingredients, antibiotics, or known or suspected carcinogens;

(6) develop and release guidelines “under notice and comment provisions” if FDA intends to allow the use of extrapolated data in aquarium drug applications under the minor species provisions of 21 CFR 514.1(d)(2); and

(7) publish NADA approvals for aquarium fish in the Federal Register and codify them in Title 21, Part 500 of the Code of Federal Regulations.

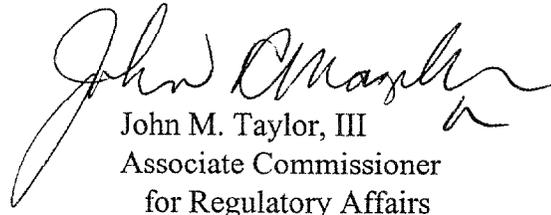
On July 15, 1994, FDA issued its response to your citizen petition. That letter served as a final response to items (1), (4), (5), (6) and (7), as presented herein. The agency deferred final comment on items (2) and (3), as we were in the process of evaluating the need for an overall enforcement policy for aquarium fish and ornamental fish drugs, including compliance with relevant CGMP's. In our July 15, 1994 response, we noted that section 512(b) of the Act and the new animal drug regulations at 21 CFR Part 514 require the submission of comprehensive NADA's for new animal drugs, with 21 CFR 514.1(b)(5) further requiring that the new animal drugs be manufactured in compliance with current good manufacturing practices. We acknowledged that while aquarium drugs marketed for the diagnosis, treatment and control of diseases in aquariums are subject to these regulations, many such drugs had been marketed without approved NADA's for years, with no enforcement action taken by FDA, pursuant to the agency's enforcement discretion. The Agency now grants items 2 and 3, in part.

Current FDA regulations still mandate the submission of NADA's for new animal drugs. As before, applications shall include, among other information, data about the new drug's chemistry, pharmacology, dosage form, clinical purpose, highlights of laboratory and clinical studies; components and composition; manufacturing methods, facilities and controls; samples; analytical methods for residues; and evidence to establish the drug's safety and effectiveness. Current CGMP's also require that new animal drugs be manufactured to ensure that purity, strength, quality and potency be maintained. Thus, to the extent that aquarium drugs, as described in your citizen petition, are submitted for NADA's, relevant safety and efficacy data, along with environmental impact and CGMP's, will be considered.

FDA's current enforcement priorities for drug use in aquaculture are detailed in the August 9, 2002 Program Policy and Procedures Manual Guide 1240.4200. Part A, *Enforcement Priorities for Drug Use in Non-Food Fish*, is of particular relevance to your citizen petition. That section explains that prior to any action regarding a drug in this category, the agency will consider its jurisdictional authority as well as the regulatory status of the drug in question (e.g., an approved new animal drug, extra-label use drug, or a drug that has been evaluated for regulatory discretion as low priority for enforcement action). For instance, drugs that are determined appropriate for regulatory enforcement

discretion are so deemed upon review of such factors as the safety status of the compound in question (including user and environmental safety) and the extent of data available for enforcement priority determinations. The potential effect on public health from the use of a particular aquaculture drug in non-food fish is a fundamental consideration in all cases. Another CVM policy guide, Program Policy and Procedures Manual Guide 1240.4240, issued October 29, 1997, discusses in detail the concept of safe levels of unapproved drugs in aquaculture. Both guides are enclosed herein.

Sincerely yours,



John M. Taylor, III
Associate Commissioner
for Regulatory Affairs

Enclosures (2)

SUPPLEMENTAL POLICIES

SAFE LEVELS OF UNAPPROVED DRUGS IN AQUACULTURE

"Safe levels of unapproved drugs" are levels of drug residue at or below which the Agency has essentially no public health concern.

These levels are established primarily as targets for developing methods for use in monitoring for residue. It is essential, in methods development, that the required sensitivity of the method be established. "Safe levels" will be determined by FDA mainly in three contexts:

- When FDA is developing a method for regulatory purposes;
- When the industry wants to develop a method for quality control/Hazard Analysis Critical Control Point (HACCP) purposes; and
- When FDA is assessing an unvalidated method that it may encounter in a regulatory context. A "safe level" would be applied only if the method is validated. This situation is expected to occur rarely.

"Safe levels of unapproved drugs" will be established only on an "as needed" basis. Such levels will not be publicized per se, but will be disclosed only in the context of methods development.

"Safe levels of unapproved drugs" are guides for prosecutorial discretion. They are not tolerances or safe concentrations, and are not binding on the Agency. The establishment of "safe levels" does not mean that FDA sanctions the use of unapproved drugs. FDA will continue to consider enforcement action against the illegal manufacture and distribution of drugs for use in aquaculture. The use of unapproved drugs, and unauthorized extralabel use of approved drugs, may also be subject to regulatory action. Under the HACCP regulations, aquaculture processors will be expected to reject fish from producers who use drugs illegally.

FDA may, however, exercise its enforcement discretion with respect to action against the aquaculture product and the drug user when the residue level is at or below the "safe level." Such an exercise recognizes, among other things, the need for the Agency to prove that the residue "may be injurious to health" when the drug cannot be proved to be a "new animal drug" by its labeling. Similarly, aquaculture processors will be permitted to accept fish with residues at or below the "safe level" as detected by a method accepted by FDA.

Establishing "Safe Levels" for Unapproved Drugs in Aquaculture: Background

- o Safe levels are generally established on the basis of toxicity data. Where toxicity data are not available, a conservative standard (e.g., 1 to 10 ppb) is used. Methods are required to be sensitive to the safe levels.
- o The Seafood HACCP regulation stresses prevention as the primary goal. Accordingly, the aquaculture drug hazard guide provides for processors' rejection of shipments from producers who use any drugs that are not sanctioned by FDA. Finished product testing (residue monitoring), therefore, is a backup means of assessing the effectiveness of the preventive measures. The guide suggests that processors themselves periodically test for drug residues.
- o For comparison:
 - FDA has established "safe levels" for residues of unapproved drugs in milk. These levels are established in the same way as described above. The States use methods under the Grade A Pasteurized Milk Ordinance for screening purposes.
 - USDA monitors for several unapproved drugs, e.g., clenbuterol and gentian violet, in meat and poultry. Any amount of residue found is considered to be violative.

Policy:

- o Safe levels and method sensitivity will continue to be established as described above.
- o Ordinarily, any amount of residue that is found will be considered to be violative. However, enforcement discretion may be exercised when residues are found at or below the safe levels.
- o FDA/CVM will continue to encourage, and provide assistance in, development of toxicology data specific to the species and drug.
- o Standards will be the same for imported and domestic samples.
- o Efforts to adopt international agreements (regional or country-by-country) will be emphasized.

ENFORCEMENT PRIORITIES FOR DRUG USE IN AQUACULTURE**PART A****ENFORCEMENT PRIORITIES FOR DRUG USE IN NON-FOOD FISH****I. Purpose:**

This guide describes enforcement priorities that apply to drugs for use in aquaculture non-food species/populations.

II. Definitions

Non-food fish - An aquaculture species is presumed to be a non-food species if it is reasonably likely that a) no significant percentage of the species population will be consumed directly or indirectly by humans for food, or b) the fish species is not known to be consumed by an identifiable human population. The following definitions are provided for categories of non-food fish.

Ornamental and aquarium fish - In general, ornamental and aquarium species are non-food species. Ornamental and aquarium fish are defined as: fish that are produced and maintained solely for exhibit purposes in home or public aquaria, or in ornamental garden ponds. (Policy and Procedures (P&P) GUIDE 1240.4260).

Baitfish – Fish commercially raised to be used as bait in sport or commercial fishing e.g., fathead minnows, golden shiners and goldfish. A baitfish species will be considered a food fish if humans will consume any significant part of the species directly or indirectly.

Home aquarium - An aquarium in a private residence or exhibited in a business for hobby or decorative purposes.

Ornamental garden pond - Pond on the property of a private residence or for display in a business for hobby or decorative purposes.

Commercial pond – Pond/ raceway where the fish are grown ultimately to be sold to individuals at pet stores or for some other commercial use.

III. Regulation of Drug Use in Non-Food Species

When CVM personnel in Division of Compliance are asked questions or receive inquiries regarding the use of compounds in non-food fish they need to:

- A. Determine which Agency or Food and Drug Administration (FDA) Center has jurisdiction for the regulation of the product based on the following categories:
1. The compound is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animal; and intended to affect the structure or any function of the body of man or other animals. The compound is a **drug** and is under the jurisdiction of FDA, Center for Veterinary Medicine (CVM). [Federal Food, Drug and Cosmetic Act (FFDCA), 201(g).] [Go to Section III B]. If the compound is determined to be a drug under FFDCA it is a drug even if it has pesticide, biologic, food or color additive properties or claims.
 2. The compound is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, or any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant. [Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)] The compound is a **pesticide** and is under the jurisdiction of the Environmental Protection Agency (EPA). Contact EPA, Office of Pesticides.
 3. The compound is a virus, serum, toxin (excluding substances that are selectively toxic to microorganisms, e.g., antibiotics), or analogous product at any stage of production, shipment, distribution, or sale, which is intended for use in the treatment of animals and which acts primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. (9 CFR 101.2) The compound is a **biologic** and is under the jurisdiction of USDA, Animal and Plant Health Inspection Service (APHIS), Center for Veterinary Biologics (CVB). Contact USDA APHIS CVB.
 4. The compound is a substance with the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of, or otherwise affecting the characteristics of any food for man or animals. (FFDCA 201 (s)) The compound is a **food additive** and is under the jurisdiction of the FDA CVM. Contact FDA, CVM, Division of Animal Feeds.
 5. The compound is a substance which is capable of coloring food, and its use or intended use is not for a purpose other than coloring. (FFDCA 201 (t)) The compound is a **color additive** and is under the jurisdiction of the FDA Center for

Food Safety and Applied Nutrition (CFSAN). Contact FDA CFSAN.

- B. Decide the regulatory status. CVM will use the following categories to determine the regulatory status of a drug:
1. **Approved new animal drug** - An approved New Animal Drug Application (NADA) exists for this indication. Refer to 21 Code of Federal Regulations (CFR) Part 514. Product is used according to label directions.
 2. **Investigational New Animal Drug (INAD)** - A potential sponsor may request an INAD exemption for collecting data to support a new animal drug approval. Contact the CVM Aquaculture Drugs Team, HFV-131.
 3. **Extra-label use drug - Use of an FDA - approved drug** under the provisions of Animal Medicinal Drug Use Clarification Act (AMDUCA). See 21 CFR 530.
 4. **Extra-label use of medicated feeds** - Provisions for the use of approved medicated feeds for minor species are explained in the Compliance Policy Guide(CPG) for Extra-label Use of Medicated Feeds for Minor Species. Compliance Policy Guide, Chapter 6, Section 615.115.
 5. **Regulatory discretion** - Drugs that have been evaluated for regulatory discretion as low priority for enforcement action (INADs/NADAs will not be required). See Low Regulatory Priority (LRP) list in Part C of this guide. For others not on the list go to Part A, Section IV of this guide.

IV. Factors to Consider for Regulatory Discretion

Division of Compliance evaluates the potential for regulatory discretion. Drugs will be categorized at CVM's initiative or on request of an interested party. In the latter case, the requestor will be asked to provide available data and information that the Center can use to determine enforcement priority. The criteria used in this determination are as follows:

- A. The safety status of the compound including:
1. User safety – Contact the Division of Human Food Safety, HFV-150.

High priority are:

- a. known or suspected carcinogens;
 - b. known serious toxicological hazards;
 - c. and suspected serious toxicological hazards believed to have substantial use in aquaculture.
2. Environmental safety – Contact the Environmental Assessment Team, HFV-145. Considerations include:
 - a. potential public or ecological safety issues including:
 - (1) potential for surface or groundwater contamination;
 - (2) known serious human toxicological hazard; and
 - (3) known serious toxicological hazard to aquatic organisms including fish, insects, and birds.
 - (2) compliance with applicable Federal, State, and local environmental laws.

B. Extent of data available for enforcement priority determinations -

In general, only published peer-reviewed studies or literature will be reviewed for the purpose of making enforcement priority determinations. However, unpublished data may be reviewed for enforcement priority determinations on a case-by-case basis. Areas to be reviewed include:

1. Human Food Safety;
2. Target animal safety and effectiveness;
3. Environmental safety; and
4. Human user and occupational safety.

V. Factors to Consider for Enforcement Priorities

- A. In general, regulatory action may be considered in any case where a high enforcement priority drug (see section V.C.) is found. In addition, high enforcement priority drugs may be the subjects of special assignments to the Field. Other drugs

will be subject to regulatory action on a case-by-case basis, based on the factors listed below.

1. Jurisdiction – (see Part A, Section III A of this guide)
2. Approval status of the active ingredient -
 - a. If FDA has withdrawn the approval of the active ingredient for reasons other than human food safety, priority will be determined on a case-by-case basis.
 - b. If an approved animal drug product containing the same active ingredient is available, the drug will ordinarily not be considered a low enforcement priority to protect the marketing of the approved product.
3. Approval or LRP status of drugs with different active ingredients but similar uses -
 - a. If an approved animal drug product containing a different active ingredient but for a similar use is available, then the drug will ordinarily not be considered a low enforcement priority to protect the marketing of the approved product.
 - a. If an animal drug product containing a different active ingredient but for a similar use as a drug is included on the LRP list (see Part C of this guide), then the drug under consideration will ordinarily not be considered a low enforcement priority.
4. The presence or absence of any significant safety or effectiveness concern as established by the available data will determine the enforcement priority. These data will include information about the active ingredient, formulation, and proposed conditions of use.
5. Products with a known potential for diversion, either directly to humans (e.g., anabolic steroids) or to food-producing species should be considered for high priority.
6. Regulatory considerations include:
 - a. potential effect on public health;
 - b. availability of expert support for a court case;

- c. availability of agency resources to support a regulatory action;
- d. egregiousness of the violative action; and
- e. availability of the required evidence.

B. Enforcement Priorities by Segment of Industry

II. Priorities for Regulation of Drug Use in Food Species/Populations:

A. Enforcement Priorities by Segment of Industry.

1. Drug Manufacturers:

(a) Primary focus among drug manufacturers and distributors will be on firms that specialize in manufacturing for, and distributing to, the aquaculture industry. Special attention should be given to:

- (1) distribution of high priority drugs;
 - (2) possible diversion and abuse situations, e.g., promotion for food species use of drugs labeled for nonfood species; and packaging of "nonfood fish" drugs in commercial pond-size containers.
- b. If intended drug use of a multi-purpose chemical is not established by labeling, or by overt acts by the vendor (e.g., promotion), enforcement actions against the vendor would have to be based on case-by-case analysis. See 21 CFR 201.128.

c. All products granted low enforcement priority must:

- (1) be labeled "For Non-food Fish Only" in a prominent place on the label;;
- (2) have adequate directions for use: and
- (3) be drug listed per 21 CFR 207.

d. Manufacturers must:

(1) be registered: and

(2) follow Current Good Manufacturing Practices (CGMPs) per 21 CFR 210 & 211.

2. Feed Manufacturers:

Priorities will be determined on a case-by-case basis. For firms required to be licensed to manufacture medicated feeds and veterinary feed directive drugs, inspections and enforcement actions will be handled according to relevant compliance guidelines.

Extra-label use of medicated feeds is prohibited under the Animal Medicinal Drug Use Clarification Act. See 21 CFR 530. However, regulatory discretion is allowed for extra-label use of medicated feeds in minor species, including fish, under a Compliance Policy Guide. See CPG 615-115. Note that for extra-label use in aquatic species, the medicated feed must already be approved for use in another aquatic species and may not be reformulated.

3. Producers:

Primary objective with producers will be on education with emphasis on proper drug usage, e.g., which drugs are permitted and under what conditions. There will be no routine inspections for enforcement purposes. This will not preclude "for-cause" inspections or surveys to determine usage patterns for drugs, sources of the drugs, etc.

"For cause" inspection assignments will encompass either individual producers, or could be more broadly based. Such inspections might include, for example, a situation in which there is reason to believe that producers might be holding significant quantities of a drug of high enforcement priority (such as malachite green) and regulation at the manufacturer/distributor level is not feasible.

PART B

ENFORCEMENT PRIORITIES FOR DRUG USE IN FOOD FISH
AND SHELFISHI. Purpose

This part of this guide describes enforcement priorities that apply to drugs for use in aquaculture food species, fin fish or shellfish.

II. Definitions

Food fish and shellfish for human consumption - An aquaculture species is presumed to be a food species if it is reasonably likely that a) a significant percentage of the species population will be consumed directly or indirectly by humans for food, or b) the species is consumed by an identifiable human population.

Food fish and shellfish for animal feed - fish used in whole or in part as a component of any animal feed will be considered a food fish species.

III. Regulation of Drug Use in Food Species, both fin fish and shellfish

When CVM personnel in Division of Compliance are faced with inquiries regarding the use of compounds in food fish (fin fish and shellfish) they need to:

- A. Determine which Agency or Food and Drug Administration (FDA) Center has jurisdiction for the regulation of the product based on the following categories:
 1. The compound is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animal; and intended to affect the structure or any function of the body of man or other animals. The compound is a **drug** and is under the jurisdiction of FDA, CVM. [Federal Food, Drug and Cosmetic Act (FFDCA), 201(g).] [Go to Section III B]. If the compound is determined to be a drug under FFDCA it is a drug even if it has pesticide, biologic, food or color additive properties or claims.
 2. The compound is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, or any substance or mixture of substances intended for use as a plant regulator, defoliant, or

desiccant. [Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)]
The compound is a **pesticide** and is under the jurisdiction of the
Environmental Protection Agency (EPA). Contact EPA, Office of Pesticides.

3. The compound is a virus, serum, toxin (excluding substances that are selectively toxic to microorganisms, e.g., antibiotics), or analogous product at any stage of production, shipment, distribution, or sale, which is intended for use in the treatment of animals and which acts primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. (9 CFR 101.2) The compound is a **biologic** and is under the jurisdiction of USDA, Animal and Plant Health Inspection Service (APHIS), Center for Veterinary Biologics (CVB). Contact USDA APHIS CVB.
4. The compound is a substance with the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of, or otherwise affecting the characteristics of any food for humans or animals. (FFDCA 201 (s)) The compound is a **food additive** and is under the jurisdiction of the FDA, CVM. Contact FDA CVM, Division of Animal Feeds.
5. The compound is a substance which is capable of coloring food, and its use or intended use is not for a purpose other than coloring. (FFDCA 201 (t)) The compound is a **color additive** and is under the jurisdiction of the FDA Center for Food Safety and Applied Nutrition (CFSAN). Contact FDA CFSAN.

- B. Decide the regulatory status. CVM will use the following categories to determine the regulatory status of a drug:
1. **Approved new animal drug** - An approved New Animal Drug Application (NADA) exists for this indication. Refer to 21 Code of Federal Regulations (CFR) Part 514. Product is used according to label directions.
 2. **Investigational New Animal Drug (INAD)** - A potential sponsor may request an INAD exemption for collecting data to support a new animal drug approval. Contact the CVM Aquaculture Drugs Team, HFV-131.
 3. **Extra-label use drug** - Use of an FDA-approved drug under the provisions of Animal Medicinal Drug Use Clarification Act (AMDUCA). See 21 CFR 530.
 4. **Extra-label use of medicated feeds** - Provisions for the use of approved medicated feeds for minor species are explained in the Compliance Policy Guide(CPG) for Extra-label Use of Medicated Feeds for Minor Species. Compliance Policy Guide, Chapter 6, Section 615.115.
 5. **Regulatory discretion** - Drugs that have been evaluated for regulatory discretion as low priority for enforcement action (INADs/NADAs will not be required). See Low Regulatory Priority (LRP) list in Part C of this guide. For others not on the list go to Part A, Section IV of this guide.

IV. Factors to Consider for Regulatory Discretion

Division of Compliance evaluates the potential for regulatory discretion. Drugs will be categorized at CVM's initiative or on request of an interested party. In the latter case, the requestor will be asked to provide available data and information that the Center can use to determine enforcement priority. The criteria used in this determination are as follows:

- A. The safety status of the compound including:
1. Human Food Safety – Contact the Division of Human Food Safety, HFV-150. High priority are:
 - a. known or suspected carcinogens;
 - b. known serious toxicological hazards;
 - c. suspected serious toxicological hazards believed to have substantial use in

- aquaculture; and
 - d. antimicrobials likely to confer bacterial resistance to drugs used in human medicine.
2. User safety – Contact the Division of Human Food Safety, HFV-150. High priority are:
- 1. known or suspected carcinogens;
 - 2. known serious toxicological hazards; and
 - 3. suspected serious toxicological hazards believed to have substantial use in aquaculture.
3. Environmental safety – Contact the Environmental Assessment Team, HFV-145. Considerations include:
- a. potential public or ecological safety issues including:
 - (1) potential for surface or groundwater contamination;
 - (2) known serious human toxicological hazard; and
 - (3) known serious toxicological hazard to aquatic organisms including fish, insects, and birds.
 - b. compliance with applicable Federal, State, and local environmental laws.
- B. Extent of data available for enforcement priority determinations -
- In general, only published peer-reviewed studies or literature will be reviewed for the purpose of making enforcement priority determinations. However, unpublished data may be reviewed for enforcement priority determinations on a case-by-case basis. Areas to be reviewed include:
- 1. Human food safety;
 - 2. Target animal safety and effectiveness;
 - 3. Environmental safety; and
 - 4. Human user and occupational safety.

V. Factors to Consider for Enforcement Priorities

- A. In general, regulatory action may be considered in any case where a high enforcement priority drug (see section V.C.) is found. In addition, high enforcement priority drugs may be the subjects of special assignments to the Field. Other drugs will be subject to regulatory action on a case-by-case basis, based on the factors listed below.
1. Jurisdiction – (see Part A, Section III A of this guide)
 2. Approval status of the active ingredient -
 - a. If FDA has withdrawn the approval of the active ingredient for human food safety reasons regulatory discretion will not normally be granted.
 - b. If FDA has withdrawn the approval of the active ingredient for reasons other than food safety reasons regulatory discretion will be determined on a case-by-case basis.
 - c. If an approved animal drug product containing the same active ingredient is available, the drug will ordinarily not be considered a low enforcement priority to protect the marketing of the approved product.
 3. Approval or LRP status of drugs with different active ingredients but similar uses -
 - a. If an approved animal drug product containing a different active ingredient but for a similar use is available, then the drug will ordinarily not be considered a low enforcement priority to protect the marketing of the approved product.
 - b. If an animal drug product containing a different active ingredient but for a similar use as a drug is included on the LRP list (see Part C of this guide), then the drug under consideration will ordinarily not be considered a low enforcement priority.
 4. If the treated fish are intended for use in animal feed, then there is a higher concern if the feed is to be used for food-producing animals. The method of feed preparation should also be considered, e.g., rendering vs. fish or fish parts.

5. The presence or absence of any significant safety or effectiveness concern as established by the available data will determine the enforcement priority. These data will include information about the active ingredient, formulation, and proposed conditions of use.
6. Regulatory considerations include:
 - a. potential effect on public health;
 - b. availability of expert support for a court case;
 - c. availability of agency resources to support a regulatory action;
 - d. egregiousness of the violative action; and
 - e. availability of the required evidence.

B. Enforcement Priorities by Segment of Industry

1. Drug Manufacturers -

- a. Primary focus among drug manufacturers and distributors will be on firms that specialize in manufacturing for, and distributing to, the aquaculture industry. Special attention should be given to:
 - (1) distribution of high priority drugs; and
 - (2) abuse situations, e.g., promotion for food species use of drugs labeled for non-food species and packaging of "non-food fish" drugs in commercial pond-size containers.
- b. If intended drug use of a multi-purpose chemical is not established by labeling, or by overt acts by the vendor (e.g., promotion), enforcement actions against the vendor should be based on case-by-case analysis. See 21 CFR 201.128.
 - a. All products granted low enforcement priority must:
 - (1) have adequate directions for use; and
 - (2) be drug listed per 21 CFR 207.
 - d. Manufacturers must:

- (1) be registered;
- (2) be drug listed per 21 CFR 207; and
- (3) follow Current Good Manufacturing Practices (CGMPs) per 21 CFR 210 & 211.

2. Feed Manufacturers -

For firms required to be licensed to manufacture medicated feeds and veterinary feed directive drugs, inspections and enforcement actions will be handled according to relevant compliance guides.

Extra-label use of medicated feeds is prohibited under the Animal Medicinal Drug Use Clarification Act. See 21 CFR 530. However, regulatory discretion is allowed for extra-label use of medicated feeds in minor species, including fish, under a Compliance Policy Guide. See CPG 615-115. Note that for extra-label use in an aquatic species, the medicated feed must already be approved for use in another aquatic species and may not be reformulated.

3. Producers -

Primary emphasis with producers will be on education with emphasis on proper drug usage, e.g., which drugs are permitted and under what conditions. There will be no routine inspections for enforcement purposes. This will not preclude "for-cause" inspections or surveys to determine usage patterns for drugs, sources of the drugs, etc.

"For cause" inspection assignments will encompass either individual producers, or could be more broadly based. Such inspections might include, for example, a situation in which there is reason to believe that producers might be holding significant quantities of a drug of high enforcement priority (such as malachite green) and regulation at the manufacturer/distributor level is not feasible.

PART C

ENFORCEMENT PRIORITIES

I. LOW REGULATORY PRIORITY AQUACULTURE DRUGS

The following compounds have undergone review by the Food and Drug Administration and have been determined to be new animal drugs of low regulatory priority.

ACETIC ACID - 1000 to 2000 ppm dip for 1 to 10 minutes as a parasiticide for fish.

CALCIUM CHLORIDE - Used to increase water calcium concentration to ensure proper egg hardening. Dosages used would be those necessary to raise calcium concentration to 10-20 ppm CaCO₃.

- Used up to 150 ppm indefinitely to increase the hardness of water for holding and transporting fish in order to enable fish to maintain osmotic balance.

CALCIUM OXIDE - Used as an external protozoacide for fingerlings to adult fish at a concentration of 2000 mg/L for 5 seconds.

CARBON DIOXIDE GAS - For anesthetic purposes in cold, cool, and warm water fish.

FULLER'S EARTH - Used to reduce the adhesiveness of fish eggs to improve hatchability.

GARLIC (Whole Form) - Used for control of helminth and sea lice infestations of marine salmonids at all life stages.

HYDROGEN PEROXIDE - Used at 250-500 mg/L to control fungi on all species and life stages of fish, including eggs.

ICE - Used to reduce metabolic rate of fish during transport.

MAGNESIUM SULFATE - Used to treat external monogenic trematode infestations and external crustacean infestations in fish at all life stages. Used in all freshwater species. Fish are immersed in a 30,000 mg MgSO₄/L and 7000 mg NaCl/L solutions for 5 to 10 minutes.

ONION (Whole Form) - Used to treat external crustacean parasites, and to deter sea lice from infesting external surface of salmonids at all life stages.

PAPAIN - Use of a 0.2% solution in removing the gelatinous matrix of fish egg masses in order to improve hatchability and decrease the incidence of disease.

POTASSIUM CHLORIDE - Used as an aid in osmoregulation; relieves stress and prevents shock. Dosages used would be those necessary to increase chloride ion concentration to 10-2000 mg/L.

POVIDONE IODINE - 100 ppm solution for 10 minutes as an egg surface disinfectant during and after water hardening.

SODIUM BICARBONATE - 142-642 ppm for 5 minutes as a means of introducing carbon dioxide into the water to anesthetize fish.

SODIUM CHLORIDE - 0.5% to 1.0% solution for an indefinite period as an osmoregulatory aid for the relief of stress and prevention of shock; and 3% solution for 10 to 30 minutes as a parasiticide.

SODIUM SULFITE - 15% solution for 5 to 8 minutes to treat eggs in order to improve their hatchability.

THIAMINE HYDROCHLORIDE - Used to prevent or treat thiamine deficiency in salmonids. Eggs are immersed in an aqueous solution of up to 100 ppm for up to four hours during water hardening. Sac fry are immersed in an aqueous solution of up to 1,000 ppm for up to one hour.

UREA and TANNIC ACID - Used to denature the adhesive component of fish eggs at concentrations of 15g urea and 20g NaCl/5 liters of water for approximately 6 minutes, followed by a separate solution of 0.75g tannic acid/5 liters of water for an additional 6 minutes. These amounts will treat approximately 400,000 eggs.

The Agency is unlikely to object to the use of these substances if the following conditions are met:

- (1) The substances are used for these indications;
- (2) The substances are used at the prescribed levels;
- (3) The substances are used according to good management practices;
- (4) The product is of an appropriate grade for use in food animals, and

(5) There is not likely to be an adverse effect on the environment.

The Agency's enforcement position on the use of these substances should not be considered an approval nor an affirmation of their safety and effectiveness. Based on the information available at some time in the future, the Agency may take a different position on the use of any or all of these substances.

Classification of these substances as new animal drugs of low regulatory priority does not exempt facilities from complying with other Federal, State, and local environmental requirements. For example, facilities using these substances would still be required to comply with National Pollutant Discharge Elimination System (NPDES) requirements.

NOTE: The primary long range goals in enforcement prioritization will be to protect public health and encourage submission of INADs and NADAs with a view toward obtaining approvals to meet therapeutic and production needs in aquaculture.

(6) Labeling and GMPs for Low Priority Drugs.

- a. Labeling for low priority use will not be required for a chemical that is commonly used for nondrug purposes even if the manufacturer or distributor promotes the chemical for the permitted low priority use.
2. However, a chemical that has significant animal or human drug uses in addition to the low priority aquaculture use will be required to be labeled for the low priority uses if the manufacturer or distributor establishes the intended low priority use for its product by promotion or other means.
- c. Where labeling is required, all other provisions of the Act pertaining to drugs except the approval requirement will apply. This includes registration, drug listing and Current Good Manufacturing Practices (CGMPs), etc.
- d.. Low regulatory priority compounds may be marketed for aquaculture use with drug claims (the claims permitted for such compounds) but must be of an appropriate quality for use in food animals.
- e. If drug claims appear on the product label, in product catalogs, or in promotional material, the following conditions must be met:
 - o The product must have been manufactured according to CGMPs as defined in 21 CFR

210 & 211;

- o The product manufacturer must be registered with the FDA; and
 - o The product must be drug-listed with FDA.
- f. Material deviations in labeling or promotion from the permitted low priority claims might cause a particular product to be removed from the low priority category.

II. SPECIAL CATEGORY

Products found not to be low regulatory priority but regulatory action deferred pending further study:

Copper sulfate

Potassium permanganate

III. EXAMPLES OF DRUGS WITH HIGH ENFORCEMENT PRIORITY

Chloramphenicol

Nitrofurans

Fluoroquinolones and Quinolones

Malachite Green

Steroid Hormones