

Drugs Used in the US Aquaculture Industry

Summary

The use of drugs and chemicals by the US aquaculture industry is strictly regulated by the US Food and Drug Administration (FDA) and the US Environmental Protection Agency (EPA). FDA requires a scientific evaluation of a drug's effectiveness and safety for humans and the environment before approval. The EPA requires a scientific evaluation of a chemical's safety before it can be registered and sold.

In the US, there are only six drugs approved for use in aquaculture: one anesthetic, one parasiticide, one spawning agent, and three antibiotics. One of the approved antibiotics is no longer manufactured and available. All drugs must be used according to label instructions.

Oxytetracycline and a potentiated sulfonamide (sulfadimethoxine: ormetoprim) are antibiotics approved for use to treat disease but only in certain types of aquatic animal (channel catfish, salmonids and lobster with oxytetracycline) and only to treat certain diseases. Antibiotics are only approved to treat disease and cannot be used as a growth promoter or prophylactically. Survey results indicate only 50,000 to 70,000 lbs of antibiotic active ingredient are sold per year for use in the domestic aquaculture industry. This represents approximately 0.3-0.4 % of all the antibiotics used in animal agriculture in the US. There is little scientific documentation to support suggestions that the domestic use of antibiotics in the aquaculture industry has caused any harm to humans or the environment.

Copper sulfate is a chemical algacide registered by the EPA for this purpose. It also has therapeutic value to treat protozoal parasite infestations of various aquatic animals. The discharge of copper sulfate is regulated by the EPA. Discharges must meet water quality standards as specified in the US Clean Water Act.

Introduction

The choice of drugs and chemicals used in the US aquaculture industry is strictly regulated by various federal and state statute, rules, regulations and guidance. Drugs used must be approved by the US Food and Drug Administration (FDA) within the confines of the Federal Food Drug and Cosmetic Act (FFDCA; 21 U.S.C. 301-392). Chemicals or pesticides used must be approved by the US Environmental Protection Agency (EPA). Pesticides are regulated under the FFDCA and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; 7 U.S.C. 136-136y). The FFDCA authorizes EPA to set legally enforceable limits or tolerances for pesticide residues in foods. Foods containing a pesticide for which there is no tolerance established, or in which a pesticide in the food exceeds the established tolerance, is considered adulterated and subject to seizure. Under FIFRA, all pesticides must be registered with EPA before they may be sold or distributed in commerce. Both the FDA and EPA base their regulatory approval or

registration decisions on the basis of various rigorous scientific evaluations that demonstrate efficacy, safety and environmental protection. The EPA also regulates pesticide discharge through provisions of the Federal Water Pollution Control Act (33 U.S.C. 1251-1387), most commonly known as the Clean Water Act. The discharge of pesticides and other potential pollutants from aquaculture facilities is regulated through the National Pollutant Discharge Elimination System (NPDES) permit. The NPDES permitting system is managed by the states or in some cases by regional EPA offices. States are required to establish water quality standards that at a minimum meet Clean Water Act requirements. States may also set limits that are more stringent than federal limits. These sets of federal and state requirements and standards ultimately limit the availability of drugs used in domestic aquaculture.

In this presentation we will identify the drugs federally approved for use in the US aquaculture industry and we will examine their use limitations. Since antibiotics are drugs of particular public concern we will also provide estimates of the volume of antibiotics used in the domestic industry. We will discuss one of the more commonly used chemicals, copper sulfate, because it also has therapeutic value. Finally, the use of drugs in aquaculture outside the US will be briefly described.

US Aquaculture Drugs

The FDCA defines a drug to mean articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the US, or official National Formulary. Generally a drug is an article intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. It includes an article, other than food, that is intended to affect the structure or any function of the body of man or other animal, and includes articles that are intended for use as a component of a drug. For aquatic animal production, articles such as ice, oxygen and salt are, by definition, drugs.

The FDA has only approved six different drugs for use in domestic aquaculture. These are listed below along with their New Animal Drug Application (NADA) or Abbreviated New Animal Drug Application (ANADA) number, and their uses are defined (particular discussion is made about antibiotics):

- Chorulon® (NADA 140-927)
- Fiquel® (NADA 042-427)
- Tricaine-S (ANADA 200-226)
- Formalin-F® (NADA 137-687)
- Paracide-F® (NADA 140-831)
- Parasite-S® (NADA 140-989)
- Terramycin® (NADA 038-439)
- Romet-30® (NADA 125-933)
- Sulfamerazine (NADA 033-950)

Chorulon® (chorionic gonadotropin) is a prescription product that is used as an aid in improving spawning function in male and female brood finfish. As a prescription product, federal law restricts this drug to use by or on the order of a licensed veterinarian. Chorulon® is used in individual fish by injecting intramuscularly just ventral to the dorsal fin. The dosage is dependent upon fish species and body weight of the individual fish. Chorulon® is sponsored by Intervet America, Inc.

Finquel® (Argent Laboratories) and **Tricaine-S** (Western Chemical, Inc.) are the same drug (MS-222; tricaine methane sulfonate) but sponsored and manufactured by different companies. MS-222 is intended for the temporary immobilization of fish, amphibians, and other aquatic, cold-blooded animals. Aquatic animals are immersed in water containing the drug at concentrations ranging from 10 to 1,000 mg/L. For food animals there is a mandatory 21 day withdrawal time before the fish can be harvested for human or animal consumption. Further, when used in food fish, use is restricted to fish from the Ictaluridae, Salmonidae, Esocidae, and Percidae families. For non-food aquatic animals it can only be used under laboratory or hatchery conditions. MS-222 must be used at water temperatures above 10 ° C (50° F). The drug does not require a veterinary prescription and is available over-the-counter (OTC).

Formalin-F® (Natchez Animal Supply Co.), **Paracide-F®** (Argent Laboratories), and **Parasite-S®** (Western Chemical) are the same drug (formalin) but sponsored and manufactured by different companies. Western Chemical has the broader drug application for formalin since their application applies to all finfish, all finfish eggs, and penaeid shrimp. Formalin-F and Paracide-F are restricted to use in salmon, trout, catfish, bluegill, and largemouth bass. Formalin is used as an external parasiticide to control protozoan parasites *Chilodonella*, *Costia (Ichthyobodo)*, *Epistylis*, *Ichthyophthirius*, *Scyphidia*, *Trichodina*, and monogenetic trematodes (*Cleidodiscus*, *Dactylogyrus*, and *Gyrodactylus* spp.). For finfish eggs, the drug is used to control fungi and for penaeid shrimp it is used to control protozoan parasites (*Bodo*, *Epistylis* and *Zoothamnium* spp.). There is no mandatory withdrawal time prior to food or non-food animal harvest (formalin does not bioaccumulate above natural background concentrations in animals) and there is no prescription required. Formalin is added to ambient water at 15 to 25 µl/L to treat finfish for up to one hour, and 1000 to 2000 µl/L for 15 minutes to treat eggs. Penaeid shrimp treatment varies with farming practice.

Antibiotics

In the US, there are only two FDA-Center for Veterinary Medicine (CVM) approved and available antimicrobials for use in domestic aquaculture but their approvals are limited to specific food fish (catfish, salmonids and lobster) and specific diseases. These antimicrobials are oxytetracycline (Terramycin® for Fish; oxytetracycline monoalkyl trimethyl ammonium) and a potentiated sulfonamide (Romet-30®; ormetoprim: sulfadimethoxine). These drugs can only be administered through feed in a specific feed formulation. A third antimicrobial is approved for use in to treat specific diseases in specific types of farm raised finfish, sulfamerazine, but is not currently available or manufactured by the sponsor, Alpharma Animal Health. The species and use limitations on these drugs exist because the safety of the antimicrobial in the approved aquatic animals, their effectiveness to cure the diseases they are approved for and their environmental safety have been satisfactorily demonstrated to FDA by the drug sponsor.

Terramycin® for Fish is the trade name for the only approved oxytetracycline product for use in aquaculture and it is approved to treat only certain diseases in catfish, salmonids and lobster. Oxytetracycline medicated feed can be used to treat bacterial hemorrhagic septicemia and pseudomonas disease in catfish at a dose of 2.5-3.75 g/100 lb (2.5-3.75 g/45.36 kg) of fish/day for 10 days when the water temperature is above 62 ° F (16.7° C). For salmonids, when the water temperature is above 48.2° F (9° C), Terramycin® for Fish can be used to control ulcer disease, furunculosis, bacterial hemorrhagic septicemia and pseudomonas disease using the same dose and duration as for catfish. Terramycin® for Fish is not currently approved for use in salmonids

at temperatures below 9° C although efforts are ongoing to provide data that could ultimately lead to CVM approval for use at these colder water temperatures. Lobster can be treated with Terramycin® for Fish to cure the bacterial disease gaffkemia. The treatment duration is only 5 days at 1 g/lb (1 g/0.4536 kg) of medicated feed. This product has a withdrawal time of 21 days for catfish and salmonids and 30 days for lobster. The CVM withdrawal time is the period between the last administration of the drug to the aquatic animal and the time when the aquatic animal can be harvested and offered for food (human or animal). The withdrawal time ensures no harmful drug residues are present when the animal is harvested for human consumption.

Romet-30® can be used in medicated feed to treat enteric septicemia of catfish and furunculosis in salmonids. The dose is 50 mg/kg (50mg/2.205 lb) body weight/day for five days. In catfish there is a 3-day mandatory withdrawal time and for salmonids, a 42-day withdrawal time. The shorter withdrawal time for catfish occurs because any Romet-30 residues that might be present are removed with the skin of catfish during processing.

There is only one approved antibiotic for ornamental fish (Nifurpirinol: Furanace Caps) held in an aquarium for treatment of columnaris disease in freshwater ornamental fish that are not reproducing. There are no other antibiotics approved for aquatic non-food animals.

It is illegal to use antibiotics prophylactically to prevent aquatic animal disease or for production purposes such as to promote aquatic animal growth. Top dressing feed with an antimicrobial (adding the antibiotic on top of the animal's normal rations) is specifically not permitted. Antibiotics have not been approved for hauling tanks or for immersion treatment of aquatic animals.

Extra-label use

There are some very limited circumstances where Terramycin® or Romet-30® medicated feed can be used for other aquatic animals. This is extra-label use. Extra-label use means use of a drug in an animal that is not in accordance with approved labeling. While the FFDCA does not permit extra-label drug use via medicated feeds, the FDA recognizes a significant need. FDA does have some regulatory discretion that can allow extra-label use of medicated feeds under very stringent conditions. If these conditions are met, FDA is unlikely to take regulatory action. These conditions are identified in the FDA Compliance Policy Guide (Extra-label use of medicated feeds for minor species, Sec. 615.115). The Guide describes how medicated catfish or salmonid feeds might be used to treat bacterial diseases in other aquatic animals or for different bacterial diseases than currently approved. Extra-label use of medicated feed can be considered when the health of animals is threatened and suffering or death would result from failure to treat affected animals. To use a medicated feed in an extra-label manner, the following conditions must be met:

- The medicated feed is already approved for use in aquatic species. This means you can only use medicated catfish, salmonid or lobster feed.
- There is express written recommendation and oversight of an attending licensed veterinarian within the context of a valid veterinarian-client-patient relationship.
- Extra-label use can only be for therapeutic purposes, i.e. to treat a disease.
- The aquaculturist has:
 - Kept complete and accurate records of feeds received, including labels, invoices, and date fed. Records must be kept for at least one year.

- Kept a current copy of the veterinarian's written recommendation
- Instituted procedures to assure that the identity of treated animals is carefully maintained.
- Taken appropriate measures to assure that assigned timeframes for withdrawal are met and no unsafe drug residues occur in any food-producing animal.
- Used the medicated feed in accordance with federal, state, and local environmental laws and regulations.
- Followed user safety provisions.

Extra-label use of antibiotics can also be secured through a licensed veterinarian if the drug is administered via injection or bath methods. These have limited utility in commercial aquaculture but might be feasible for valuable brood stock or ornamental fishes. Some of the same provisions described above apply.

Volume Estimate

Because of the nature and very limited size of the domestic US aquaculture industry, it is possible to reliably determine the volume of antibiotics purchased and presumably used in the domestic aquaculture industry each year. While there are three antimicrobials approved by CVM for the domestic food fish aquaculture industry, only two are available (oxytetracycline and ormetoprim: sulfadimethoxine). There is only one manufacturer of oxytetracycline (Phibro Animal Health, Fairfield, NJ) and one manufacturer of ormetoprim: sulfadimethoxine (Alpharma Animal Health Division, Fort Lee, NJ).

Given this unique circumstance, it is possible to estimate the quantity of antibiotic used in the domestic industry by asking the two pharmaceutical companies the quantity of active ingredient sold to the domestic aquaculture feed industry. This has now been done. In the 25 month period from January 2001 to February 2003, there was 36,126 kg of ormetoprim: sulfadimethoxine active ingredient (A.I.) sold (Kohan 2003). Averaged out, the amount sold per year was 17,340.48 kg of ormetoprim: sulfadimethoxine as active ingredient. In 2001 there was 15,200 kg A.I. of oxytetracycline sold and in 2002, only 7,134 kg A.I. sold to the domestic aquaculture industry (Knightly 2003). The combined total is 32,540.48 kg A.I. (71,752 lbs) sold in 2001 and 24,475 kg A.I. (53,966 lbs) sold in 2002. Presumably the volume sold is equivalent to the volume used.

Inquiry of pharmaceutical companies offers the most direct and reliable method to determine the volume of antibiotics sold and presumably used in the domestic aquaculture industry but it does not capture the totality of use. Some, albeit minor use, occurs when medicated feeds are purchased in Canada for use in the US aquaculture industry. Sowles (2003) reports that in Maine, 6.7 kg AI oxytetracycline (2002) up to 349 kg A.I. oxytetracycline (2001) was used in the Atlantic salmon industry. All but 50 kg A.I. was purchased in medicated feed manufactured in Canada. Since January 2001, Maine has required monthly electronic reporting of medications and pesticides used by all salmon farmers.

These data suggest the volume of antibiotic used in the domestic aquaculture industry is very low compared to estimated volumes used in other agriculture industry sectors (Mellon et al. 2001; Carneval 2001). Carneval (2001) surveyed pharmaceutical companies to estimate the total volume of antibiotics used in animal agriculture for all purposes. In 1999, a total of 8.44 million kg of antibiotic active ingredients and 1.33 million kg of tetracyclines were used in US animal

agriculture. While not directly comparable because of timing differences, domestic aquaculture represents only about 0.3-0.4 % of the total antibiotics used and 0.5-1.14 % of the total tetracyclines used in US animal agriculture. The volume of active ingredients reported sold to the domestic aquaculture industry by manufacturer representatives is far less than speculative reports suggest. Benbrook (2002) estimated a volume up to 433,000 lbs A.I. was used per year by the domestic aquaculture industry and clearly this grossly overestimates the amount used.

Significance of antibiotic use in domestic aquaculture

The environmental and public health significance of the two antibiotics used in the domestic farm raised food fish industry is not known. The significance is dependent upon a number of factors including environmental fate and the probability that human pathogens might become resistant to the particular antibiotic or class of antibiotics. There is currently no data available to demonstrate a direct link between the use of either antibiotic in fish farming and the occurrence, even rarely, of human pathogens resistant to that particular antibiotic. There are also no publicly available reports to suggest that antibiotic residues occur in domestic farm raised fishes marketed for human consumption. MacMillan (2001) provides reasons why the public health significance of antibiotic use in the domestic industry is thought to be negligible. These reasons include the significant difference between the bacterial flora (pathogenic, commensal and environmental) of fish and humans, the difference in body temperatures between fish and humans or their environments, and various physical-chemical barriers to the transfer of resistance factors between aquatic bacteria and human bacterial pathogens.

Only very limited data exists documenting the concentration of antibiotic in water as a consequence of the use of antibiotic medicated feed. Some data has recently been collected regarding the concentration of antibiotics discharged from flow-through water raceways (Thurman et al. 2002). These studies documented very low (0-2.3 µg/L) concentrations of oxytetracycline or ormetoprim:sulfadimethoxine (0-15 µg/L) in raceway discharge waters of public hatcheries using medicated feeds to treat sick fish. The frequency of medicated feed use was not documented. It is not clear what type of waste management systems were in place at these facilities. It is believed that the type of waste treatment system utilized may impact the concentration of antibiotics in discharge water. The environmental significance of these concentrations was not investigated.

Studies are underway to determine the potential impact of oxytetracycline in the environment. The USGS's Upper Midwest Environmental Sciences Center (UMESC) is writing an amended environmental assessment for the use of oxytetracycline as an oral drug for use in US aquaculture. As part of the assessment, UMESC is developing dispersion and fate models to predict environmental concentrations of oxytetracycline resulting from use at public and commercial hatcheries. The UMESC has also developed and validated a predictive model for waterborne drugs (e.g., immersion oxytetracycline) discharged from hatcheries into public waters. The proposed model currently is being reviewed by CVM (Gaikowski 2003).

The FDA has published guidance (Guidance No. 78) and guidance (draft No. 152) that identifies the agencies approval process for antibiotics. The FDA Guidance No. 78 (Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals) document addresses how, pursuant to section 512 of the Federal Food, Drug and Cosmetic Act, FDA intends to consider the potential human health impact of the microbial effect associated with all uses of all classes of antimicrobial new animal

drugs intended for use in food-producing animals when approving such drugs. Guidance No. 152 (Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern) further explains the Agency's approach for assessing the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. The primary focus of this guidance is to address the concern that the use of antimicrobial new animal drugs in food-producing animals will cause resistance determinants or resistant bacteria to emerge and to adversely impact human health. However, additional microbiological effects of antimicrobial drugs will also be examined including pathogen load effects and effects of drug residues on human intestinal microflora.

Low Regulatory Priority Aquaculture Drugs

The FDA-CVM has established certain domestic aquaculture drugs as "low regulatory priority" drugs as listed below:

Acetic acid- 1000 to 2000 mg/L 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 mg/L CaCO₃.

Calcium oxide- used as an external protozoacide for fingerlings to adult fish at a concentration of 20000 mg/L for 5 seconds.

Carbon dioxide gas- for anesthetic purposes in cold, cool and warm water fish.

Fullers' earth- used to reduce the adhesiveness of fish eggs to improve hatchability.

Garlic (whole [bulb] form)- used for control of helminth and sea lice infestation 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 30,000 mg/L [sic] and 7,000 mg/L NaCl [sic] solutions for 5 to 10 minutes.

Onion (whole [bulb] form)- used to treat external crustacean parasites, and to deter sea lice from infesting external surface of salmonids at all life stages.

Papain- used at a 0.2% solution to remove 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 10-2,000 mg/L.

Povidone iodine - 100 mg/L solution for 10 minutes as an egg surface disinfectant during and after water hardening.

Sodium bicarbonate- 142-642 mg/L for five minutes as a means of introducing carbon dioxide into the water to anesthetize fish.

Sodium chloride [salt]- 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% [1.5%] solution for 5 to 8 minutes to treat eggs in order to improve their hatchability. (see Isaac, J., Jr. and Fries, L.T. 1991. Separation of channel catfish eggs in sodium sulfite with and without papain. The Prog. Fish-culturist 53: 200-2001.)

Thiamine hydrochloride - used to prevent or treat thiamine deficiency in salmonids. Eggs are immersed in an aqueous solution of up to 100 mg/L for up to four hours during water hardening. Sac fry are immersed in an aqueous solution of up to 1,000 mg/L for up to one hour.

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

Low regulatory drugs have been determined by FDA to be new animal drugs but they have not been approved as new animal drugs. It is unlikely a drug sponsor will come forward seeking approval of agents such as ice or sodium chloride but the FDA recognizes that these agents may have a physiological impact and are hence legitimately regarded as a “drug” by definition. FDA encourages formal approval of these drugs but regards them as low regulatory priority when they are used according to indications identified above, at the dosages identified above, are used according to good management practices, they are of appropriate grade for use in food animals, and there is not likely to be an adverse effect on the environment. Low regulatory drugs should not be confused with food ingredients that are Generally Recognized as Safe (GRAS). Low regulatory drugs, while of improbable public health or environmental significance when used according to the above FDA specifications are still drugs. They are potentially capable of affecting the structure or any function of the body of an aquatic animal. Drugs must be approved by the FDA demonstrating, among other things, that they are safe for the animal and induce the effect claimed. GRAS substances are strictly food ingredients (there is no drug claim) whose use is generally recognized by qualified experts as safe for humans. While a substance such as salt or garlic may be perfectly safe for humans when added to food, its effectiveness as a drug and its safety for fish must still be demonstrated by scientifically rigorous procedures.

Investigative New Animal Drugs (INAD)

As part of the FDA scientific data gathering requirements needed to approve a new antibiotic or other drug, an INAD exemption may be issued by FDA. The exemption allows a scientist or aquatic animal producer involved in a specific drug approval process to test the effectiveness of the drug in a commercial environment. INAD exemptions must be obtained from FDA and

entails considerable scrutiny to assure the testing will be valid and that human, animal and environmental safety is protected.

Chemicals of Therapeutic Value

Of the few chemicals used in domestic aquaculture, copper sulfate, copper sulfate pentahydrate and various chelated copper compounds are probably the most frequent. Copper sulfate is approved by EPA as an algacide. Concurrently, copper sulfate also has therapeutic properties in the control of external protozoan parasites on finfish. The FDA does not object to the proper use of a pesticide like copper sulfate if the chemical has incidental, concurrent therapeutic (drug) benefit (FDA-CVM Guide 1240.4220, 1997). EPA has registered copper sulfate for, amongst other things, the control of algae growths in impounded water, lakes, ponds, reservoirs, and irrigation and irrigation drainage conveyance systems. Copper sulfate is applied at 0.0013 to 10 mg/L for aquatic uses. At these same concentrations and depending upon water hardness, copper sulfate does have therapeutic benefit. While the EPA has exempted copper sulfate from the requirement of a tolerance in fish (Federal Register, 2000) the discharge of copper in effluents is still regulated through the federal Clean Water Act water quality standards (40 CFR 131.36) or various state standards that may be more stringent.

International Use of Drugs in Aquaculture

Use of drugs during the production of aquatic animals in other countries varies significantly. This variation occurs as a consequence of different drug approval requirements and regulatory attention. Differences in the availability of certain drug classes between countries can be dramatic. Japan, for example, has 29 individual or combination antibiotics approved for use in aquatic animals (Okamoto 1992) while the US has two. The US FDA (Young 2002) recently listed drugs used internationally in aquatic animal production that are not also approved for use in the US. Examples of drugs in use in foreign aquaculture are listed below:

- Acriflavine
- Amoxicillin
- Ampicillin
- Benzocaine
- Bicozamycin
- Chloramphenicol
- Colistin sulfate
- Doxycycline
- Erythromycin
- Florfenicol
- Flumequine
- Fosfomycin
- Fruluphenicol
- Furanace
- Furazolidone
- Josamycin
- Kanamycin
- Kitasamycin
- Lincomycin
- Malachite green

- Methylidihydrotestosterone
- Methylene blue
- Miroxisacin
- Nalidixic acid
- Nitrofurantoin
- Novobiocin
- Nifurstyrenate
- Oleandomycin
- Oxolinic acid
- Spiramycin
- Thimphenicol

Within the international community there is considerable interest in harmonizing the drug approval process and ensuring drugs used in all of animal agriculture throughout the world are used safely and without unsafe drug residues (Smith 2002). The FDA Modernization Act of 1997 specifically provides that FDA must participate with other countries to harmonize regulatory requirements.

Increasing global concern about antibiotic resistance of human pathogens is also encouraging efforts to ensure this class of drugs are not misused in foreign countries. The Food and Agriculture Organization of the UN (FAO), the World Health Organization (WHO), and the World Organization for Animal Health (OIE) are working to develop a common approach dealing with the world-wide containment of antimicrobial resistance. These groups will be advising the Codex Alimentarius Commission on possible methods to achieve this goal.

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