

Understanding Antimicrobial Resistance and Biosecurity in Aquaculture

FAO candidate Reference Centers on AMR and Aquaculture Biosecurity

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Governance and antimicrobial use in aquaculture in selected countries/regions

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Global awareness of antibiotic usage is important because antibiotic susceptibility is impacted by country and aquatic animal population



Topics for discussion under governance and use of antibiotics in each country

1. Approved antibiotics for use in a country
2. Governmental regulations
3. Growth promotion use
4. Forbidden antibiotics



Countries/regions considered

- USA
- EU
- China
- India
- Vietnam
- Africa



USA: Regulations on antimicrobial use in aquaculture

- Three antibiotics approved for food fish use: oxytetracycline, florfenicol, and ormetoprim/sulfadimethoxine
- Highly restrictive
- Regulated by US Food and Drug Administration (FDA) under the Veterinary Feed Directive Rule with intent to:
 - Reduce bacterial resistance
 - Prolong effectiveness
- Administered under veterinary supervision



USA: Use of antibiotics in food fish

- Antibiotics administered to food fish are in medicated feeds
 - Veterinary Feed Directive (VFD) Drugs
- Use of VFD drugs is ordered by a licensed veterinarian for a specific fish species and a specific disease
 - Veterinarian issues a Veterinary Feed Directive Order
 - Written statement issued by licensed veterinarian that orders the use of a VFD drug in/on animal feed.
- Growth promotion use prohibited
- Extra label drug use prohibited



USA: Veterinarian's responsibilities for use of VFD feed



Licensed and maintain valid
Veterinarian-Client-Patient Relationship (VCPR)

1. Knowledge of fish health by recent examination of fish and/or visit to farm
2. Responsibility for clinical judgement of fish health
3. Availability for follow-up care
4. Oversight for proper use of medication including preslaughter withdrawal

Prompt treatment

Proper regime according to label

5. Maintenance of medical records



This fillable form is published by the American Veterinary Medical Association, 1931 North Meacham Rd, Schaumburg, Illinois 60173. The form is provided for your convenience, and is consistent with the common format published in the Food and Drug Administration's draft Guidance for Industry #233, "Veterinary Feed Directive Common Format Questions and Answers." This form is not intended to provide legal advice or opinion and should not be construed as such. This form should be completed with all information required by applicable federal statutes and regulations related to the Veterinary Feed Directive.

Veterinary Feed Directive

Veterinarian: _____ Client: _____
Address: _____ Address: _____

Phone: _____ Phone: _____
Fax or email (optional): _____ Fax or email (optional): _____

Drug(s): _____ Drug Level: _____ g/ton Duration of Use: _____

No substitutions allowed

Species and production class: _____ **No refills/reorders authorized**
Indications for use: _____
Caution (if any): _____

USE OF FEED CONTAINING THIS VETERINARY FEED DIRECTIVE (VFD) DRUG IN A MANNER OTHER THAN AS DIRECTED ON THE LABELING (EXTRALABEL USE) IS NOT PERMITTED

Approximate number of animals: _____
Premises: _____
Other identification (e.g., age, weight) (optional): _____

Special instructions (if any): _____

Affirmation of intent (for combination VFD drugs) (mark one statement)*

(*For VFD drugs for which there are no approved VFD combinations, only the first affirmation statement should be marked)

This VFD only authorizes the use of the VFD drug(s) cited in this order and is not intended to authorize the use of such drug(s) in combination with any other animal drugs.

This VFD authorizes the use of the VFD drug(s) cited in this order in the following FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component:

Drug(s)	Drug Level(s) and Any Special Instructions

This VFD authorizes the use of the VFD drug(s) cited in this order in any FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component.

► Withdrawal time (if any): This VFD must be
withdrawn ____ days prior to slaughter ◀

VFD date of issuance (month/day/year): _____ VFD expiration date (month/day/year): _____
(As specified in the approval; cannot exceed 6 months after issuance)

Veterinarian's signature: _____
All parties must retain a copy of this VFD for 2 years after the date of issuance



Veterinarian's Responsibilities (cont'd)

- Issue VFD order in writing with ALL required information to client
- Maintain electronic or original order available for FDA inspection for 2 years



VFD feed: Farmer's (Client's) Responsibilities



Cooperate with veterinarian to maintain valid VCPR

- Follow dose rate, duration, expiration date, and withdrawal time

Maintain electronic or hard copy of VFD orders for FDA inspection for 2 years



VFD feed: Manufacturer's Responsibilities

- Register with FDA
- Possess medicated feed mill license
 - Can **manufacture** VFD feeds **without** signed order
- Maintain VFD feed manufacturing records for 1 year and available for FDA inspection
- If also distributor, maintain electronic or hard copy for FDA inspection for 2 years



USA: Antibiotics forbidden for use in food fish

High enforcement priority

- Chloramphenicol
- Fluoroquinolones and quinolones
- Nitrofurans



European Union (EU): Approved aquaculture antibiotics

Antibiotic	Class	
Florfenicol	Phenicol	
Gentamicin	Aminoglycoside	
Sarafloxacin	Quinolone	
Sulfonamides	Sulfa drug	
Tetracycline	Tetracycline	
Tilmicosin	Macrolide	
Trimetoprim	Antibacterial Folate Antagonist	

No antibiotics can be used for growth promotion



EU: Regulations on antimicrobial use in aquaculture

- Veterinary medicinal products in the EU are regulated by the “The Rules Governing Medicinal Products in the European Union” (European Medicines Agency (EMA))
- Drugs can be approved by a country (member state) or mutual recognition between states
 - Approvals and market authorization vary among member states
 - Most countries require a veterinary prescription for approved antibiotics (including medicated feed containing a premix of antibiotics)
 - EU governs mixing antibiotics in feed at mills, marketing of medicated feed and use



EU: Regulations on the extra label use of antibiotics in aquaculture

- Veterinarians can prescribe extra label under cascade system if:
- No veterinary antibiotics are authorized for disease or fish species in the country where treatment will take place
- Prescribing veterinarian takes responsibility for aquatic animals
 - Withdrawal period must be observed: minimum of 500 degree days



EU: Cascade system

- Veterinarians must always use antibiotics approved for use in food fish in accordance with regulations where treatment is to take place
- If no suitable antibiotics authorized to treat a disease, the veterinarian can treat fish in extra label manner in accordance with the EU Cascade Procedure
 - Risk-based decision tree that allows veterinarian to use clinical judgement.
 - Veterinarian should consider the summary of product characteristics (SPC)



EU: Cascade steps (preferred order): Use antibiotic according to following scheme (in decreasing order):

1. Veterinary antibiotic is authorized for indication in country (where treatment takes place)

If NO:

2. Antibiotic is authorized for another animal species or different condition in same species. *If NO:*

3. Antibiotic is authorized in country for use in humans. *If NO:*

4. Antibiotic is not authorized in country but authorized in another member state for use in any food producing animal species *If NO:*

5. Antibiotic can be imported from outside Europe via special Import Scheme

- Antibiotics used under the Cascade system are administered by prescription under supervision of registered veterinarians



EU: Antibiotics forbidden for use in food fish

- Chloramphenicol
- Nitrofurans
- EMA designation of Category A drugs (Designated as not appropriate for use in food producing animals). e.g includes antibiotic classes not authorized in veterinary medicine but authorized in human medicine in the EU. Can't be used extra label in the Cascade e.g. glycopeptides vancomycin, cephalosporins



China: Approved aquaculture antibiotics

- Twelve antibiotics have been authorized for use in Chinese aquaculture:
 - Antibiotics can only be used under the direction of a veterinarian
 - Dose rate and application can vary according to the discretion of the veterinarian
 - Use for growth promotion prohibited



China: Approved antibiotics

Preparation	Component	Classification
Thiamphenicol Powder	Thiamphenicol	Amphenicols
Florfenicol Powder	Florfenicol	
Florfenicol Injection		
Enrofloxacin Powder	Enrofloxacin	Quinolones
Magnesium Ascorbic Acid Phosphate and Ciprofloxacin Hydrochloride Premix	Ciprofloxacin	
Flumequine powder	Flumequine	
Doxycycline Hyclate Powder	Doxycycline	Tetracyclines
Neomycin Sulfate Powder	Neomycin	Aminoglycosides
Compound Sulfamonomethoxine Sodium Powder	Sulfamonomethoxine	Sulfonamides (Folic acid inhibitors)
Compound Sulfadiazine Powder	Sulfadiazine/trimethoprim	
Compound Sulfadimidine Powder	Sulfadimethoxine/trimethoprim	
Compound Sulfamethoxazole Powder	Sulfamethoxazole/trimethoprim	

Table courtesy of Dr.Qing Wang

Antibiotics can only be used under the direction of veterinarian



China: Regulations on antimicrobial use in aquaculture

- The Bureau of Fisheries, Ministry of Agriculture and Rural Affairs (MARA): makes major policy for fisheries
 - The Veterinary Bureau of the MARA: organizes and develops strategies, programs and plans for veterinary medicine and drugs including drafting laws and regulations and labeling antibiotics
 - The Veterinary Bureau licenses drug stores that sell medications for aquaculture
- 2005 Manufacturing of aquatic antibiotics performed with Good Manufacturing Practices (GMP) standards
- MARA conducts inspections in major aquaculture-producing regions to ensure regulations are followed for quality and safety of antibiotics



China: Use of antibiotics in food fish

- Oral administration usually mixed with feed by farmer is most common route
- Fish clinics in aquaculture production areas are staffed by licensed fish veterinarians
 - During disease outbreaks, farmer will consult with a licensed veterinarian who diagnoses fish disease and prescribes appropriate medication and concentration of antibiotic in feed for treatment
 - Prescriptions for authorized veterinary medicines available only from veterinarians
 - Extra label use does not appear to be an issue
 - e.g. Target disease listed as “septicemia,” fish species not specified; florfenicol for treatment of “bacterial infection,” fish species not specified
 - Use of prescribed antibiotics must be recorded and a minimal preslaughter withdrawal period observed



China: Unauthorized drugs in aquaculture

(Liu, et al., 2017)

- Amoxicillin
 - Chloramphenicol
 - Chlortetracycline
 - Tylosin
 - Pencillin G
- Nitrofurans (e.g. Furazolidone)
 - Gentamycin
 - Erythromycin
 - Oxytetracycline
 - Streptomycin



India:antimicrobials used in aquatic animals

Antibiotics	
Streptopenicillin	Beta lactams
Ampicillin	Beta lactams
Amoxicillin	Beta lactams
Benzyl penicillin	Beta lactams
Enrofloxacin	Quinolones
Oxytetracycline	Tetracyclines
Tylosin	Macrolide
Sulfamethoxazole	Sulfonamides (Folic acid inhibitors)
Trimethoprim	Inhibitor of dihydrofolate reductase

Source: Watts et al., 2017; Sorum, 2006

* Addressed in National Health Policy, 2017



India: Antibiotics for use in fish

- No antibiotics are approved for use in aquatic animals (Gaurav Rathore, 2020)
- Antibiotics: schedule H drugs sold as prescription but frequently sold by pharmacists over the counter to farmers
 - Some antibiotics used for fish labeled for terrestrial animals. No information on withdrawal times for fish.
 - Some antibiotics used for fish are labelled for human use- many are critically important



India: Regulations on antimicrobial use in aquaculture

- Oversight of antimicrobial use (AMU):
 - The Department of Animal Husbandry, Dairying and Fisheries (DAHDF)

Apex department of The Ministry of Agriculture and Farmer's Welfare (MOAFW)
 - Most staff not authorized to prescribe medicines. They are not fish veterinarians or medical practitioners.
 - Little training for veterinarians in aquatic animal health

Veterinary officers of animal husbandry department not familiar with fish health issues



India: Fish antibiotic regulations (cont'd)

- Most antibiotic use not supervised by trained government personnel – usage is based on word of mouth from other farmers, drug companies, etc.
- Approximately 190 companies manufacture antibiotics for animals
 - No data for production and sales
 - Government often fails to monitor compliance and enforce laws on unapproved products which continue to fill the market
 - Many banned antibiotics used as long as residues not detected



India: Regulations

- 2011 the Food Safety and Standards Authority of India (FSSAI) set regulations for tolerance limits for use of antibiotics which include: tetracycline, trimethoprim, oxytetracycline, and oxolinic acid
- Seafood inspected for residues by Marine Products Export Development Authority (MPEDA) - reserved for fish intended for international trade and generally not for retail trade within India



India: Antibiotics that are presently banned for use in shrimp aquaculture

Chloramphenicol

Neomycin

Nalidixic acid

Sulphamethoxazole

Metronidazole

Fluroquinolones

Glycopeptides

Nitrofurans including furaltadone, furazolidone, furylfuramide, nifuratel, nifuroxime, nifurprazine, nitrofurantoin, nitrofurazone

Sulphonamide drugs (except approved sulphadimethoxine, sulphabromomethazine and sulphaethoxypyridazine)

(Leaño, E.M. & Weimin, M. eds. 2020)



Vietnam: aquaculture antibiotics approved

• Amoxicillin	Beta lactam
• Erythromycin	Macrolide
• Florfenicol	Phenicol
• Doxycycline	Tetracycline
• Oxytetracycline	Tetracycline
• Sulphadiazine, trimethoprim	Sulfonamide
• Sulphadimethoxine, ormetoprim	Sulfonamide
• Sulphadimethoxine, trimethoprim	Sulfonamide
• Sulphadimidine, trimethoprim	Sulfonamide
• Sulphamethoxazole, trimethoprim	Sulfonamide

Vietnam: Agencies responsible for regulation of antibiotics in aquaculture

- Ministry of Agriculture and Rural development (MARD) responsible for
 - Regulation of veterinary medicines permitted for use
 - Lists of medications banned for use
 - Provisions of content labeling, testing records, production, sale, and import of veterinary drugs
 - Antibiotics in animal feed for growth promotion prohibited
- The Department of Animal Health (DAH) has responsibilities for
 - drafting/developing regulations on AMU and AMR
 - developing technical guidance on AMU and AMR
 - monitoring of AMU and AMR in aquaculture, including importation, registration and circulation of antibiotics
- The National Agro-Forestry and Fishery Quality Assurance Department (NAFIQAD) oversees a national monitoring program for chemical and antibiotic residues of aquatic animal products

Vietnam: List of antibiotics banned for use in aquaculture

Names of antibiotics (Circular No. 10/2016/TT-BNNPTNT)

- Chloramphenicol
- Metronidazole and other nitroimidazoles
- Nitrofurans (including furazolidone)
- Glycopeptides
- Fluoroquinolones
- Enrofloxacin
- Ciprofloxacin
- Sources: MARD, 2009; 2016a.



African countries: use of antimicrobials

- Most African countries have a list of approved and banned antimicrobials for food animals including fish.
- Veterinary oversight for antimicrobial use is mandated in most countries by law. However, enforcement is questionable.
- Zambia: Guidelines for antimicrobial use in aquaculture are now being developed. Currently, no antibiotic use is allowed, although some farmers incorporate them in feed (especially tetracycline)



Summary: Governance of aquaculture antibiotic usage

Country/Region	Antibiotics approved	Growth Promotion ban	Regulatory Oversight
USA	Phenicol Sulfa drugs, tetracyclines	Y	Y US FDA
EU	Phenicol Aminoglycosides, Quinolones, Macrolide Sulfa drugs, tetracyclines	Y	Y EMA
China	Aminoglycosides, quinolones, tetracyclines sulfa drugs	Y	Y The Veterinary Bureau of the MARA
India	None	N Addressed in National Health Policy, 2017 banning or restricting the use of antibiotics as growth promoters	Y MOAFW, DAHDF, FSSAI
Vietnam	Tetracyclines, macrolides Phenicol, sulpha drugs	Y	Y MARD, DAH, NAFIQAD
African countries	Mixed/under progress	Mixed policies	Limited; varies with countries



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