Fish Drug Approvals and Veterinary Feed Directives

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Today’s Topics

• Drugs approved or indexed for fish
• Extralabel use regulations and policy
• Recent change of certain products from over the counter to VFD or Rx status
• Veterinary Feed Directives (VFDs)
• Resources for Additional Information
Parts of a New Animal Drug Application

• Effectiveness
• Target Animal Safety
• Human Food Safety
• Environmental Impact
  • Manufacturing
  • Labeling
• All Other Information
APPROVED DRUGS:
Medicated Articles/Feed
<table>
<thead>
<tr>
<th>Approved products</th>
<th>Approved indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aquaflor®</strong> (florfénicol)</td>
<td>Catfish: For the control of mortality due to enteric septicemia of catfish associated with <em>Edwardsiella ictaluri</em></td>
</tr>
<tr>
<td></td>
<td>Freshwater-reared salmonids: For the control of mortality due to coldwater disease associated with <em>Flavobacterium psychrophilum</em></td>
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<tr>
<td></td>
<td>Freshwater-reared salmonids: For the control of mortality due to furunculosis associated with <em>Aeromonas salmonicida</em></td>
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<tr>
<td></td>
<td>Freshwater-reared warmwater finfish: For the control of mortality due to streptococcal septicemia associated with <em>Streptococcus iniae</em></td>
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<tr>
<td></td>
<td>Freshwater-reared finfish: For the control of mortality due to columnaris disease associated with <em>Flavobacterium columnare</em></td>
</tr>
<tr>
<td>Drug</td>
<td>用途</td>
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<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Terramycin® 200 for Fish</td>
<td>Salmonids: Control of ulcer disease caused by <em>Hemophilus piscium</em>, furunculosis caused by <em>Aeromonas salmonicida</em>, bacterial hemorrhagic septicemia caused by <em>Aeromonas liquefaciens</em>, and pseudomonas disease</td>
</tr>
<tr>
<td>(oxytetracycline dihydrate)</td>
<td>Catfish: Control of bacterial hemorrhagic septicemia caused by <em>Aeromonas liquefaciens</em>, and pseudomonas disease</td>
</tr>
<tr>
<td></td>
<td>Pacific salmon: For marking of skeletal tissue</td>
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<tr>
<td></td>
<td>Freshwater-reared salmonids: Control of mortality due to coldwater disease associated with <em>Flavobacterium psychrophilum</em></td>
</tr>
<tr>
<td>Romet-30® (Sulfadimethoxine/ormetoprim)</td>
<td>For the control of furunculosis in salmonids (trout and salmon) caused by <em>Aeromonas salmonicida</em> strains susceptible to sulfadimethoxine and ormetoprim combination</td>
</tr>
<tr>
<td></td>
<td>For control of enteric septicemia of catfish caused by <em>Edwardsiella ictaluri</em> strains susceptible to sulfadimethoxine and ormetoprim combination</td>
</tr>
<tr>
<td>Sulfamerazine Fish Grade</td>
<td>Rainbow, brook and brown trout: Control of furunculosis</td>
</tr>
<tr>
<td>(sulfamerazine)</td>
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</tr>
</tbody>
</table>
APPROVED DRUGS:
Immersion
<table>
<thead>
<tr>
<th>Approved immersion products</th>
<th>Approved indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>HALAMID® Aqua (chloramine-T)</td>
<td>For the control of mortality in freshwater-reared salmonids due to bacterial gill disease associated with <em>Flavobacterium</em> spp.</td>
</tr>
<tr>
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<td>For the control of mortality in walleye due to external columnaris disease associated with <em>Flavobacterium columnare</em></td>
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<tr>
<td></td>
<td>For the control of mortality in freshwater-reared warmwater finfish due to external columnaris disease associated with <em>Flavobacterium columnare</em></td>
</tr>
<tr>
<td></td>
<td>All finfish eggs: For the control of fungi of the family Saprolegniaceae</td>
</tr>
<tr>
<td></td>
<td>Penaeid shrimp: For the control of protozoan parasites (<em>Bodo</em> spp., <em>Epistylis</em> spp., and <em>Zoothamnium</em> spp.)</td>
</tr>
<tr>
<td>Approved immersion products</td>
<td>Approved indications</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
</tbody>
</table>
| **35% Perox-aid® (hydrogen peroxide)** | - For the control of mortality in freshwater-reared finfish eggs due to saprolegniasis  
- For the control of mortality in freshwater-reared salmonids due to bacterial gill disease associated with *Flavobacterium branchiophilum*  
- For the control of mortality in freshwater-reared coolwater finfish and channel catfish due to external columnaris disease associated with *Flavobacterium columnare* |
| **OXYmarine™**  
**Pennox 343®**  
**Terramycin 343®**  
**Tetroxy® 343**  
**Tetroxy® Aquatic (oxytetracycline HCl)** | - To mark skeletal tissues, most often the otoliths, of all finfish fry and fingerlings for subsequent identification |
| **Tricaine-S (tricaine methanesulfonate)** | - For the temporary immobilization of fish, amphibians, and other aquatic, cold-blooded animals. Use in food fish restricted to Ictaluridae, Salmonidae, Esocidae, and Percidae. |
APPROVED DRUGS:
Injectable
<table>
<thead>
<tr>
<th>Approved products</th>
<th>Approved indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorulon® (chorionic gonadotropin)</td>
<td>Aid in improving spawning function in male and female brood finfish</td>
</tr>
</tbody>
</table>
Other Categories

• Conditional Approval
• The Index of Legally Marketed Unapproved New Animal Drugs for Minor Species
• Extralabel use
Conditional Approval

- Option for minor use or minor species
  *Minor species are any animals besides: horses, dogs, cats, cattle, pigs, turkeys, and chickens*
- Meets safety standards for approval
- Reasonable expectation of effectiveness
- With annual renewals, the sponsor can market the drug for up to five years while completing effectiveness trials
- Allows early marketing to give the drug company some return on investment and makes it available for use sooner
Conditional Approval

• There are no current conditional approvals for use in fish.

• Aquaflor-CA1 was a conditional approval before the drug was fully approved for columnaris in catfish.

• Extralabel use of conditionally approved drugs is prohibited.
Indexing

• The Index of Legally Marketed Unapproved Drugs for Minor Species

• Only for non-food producing minor species; no transgenics

• Based on evaluation by an outside expert panel acceptable to CVM

• No extra-label use
## Fish Drugs on the Index

<table>
<thead>
<tr>
<th>Product</th>
<th>Active ingredient(s)</th>
<th>Intended use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovaprim</td>
<td>sGnRHa + domperidone</td>
<td>For use as a spawning aid in ornamental finfish broodstock</td>
</tr>
<tr>
<td>Aquacalm</td>
<td>metomidate hydrochloride</td>
<td>For the sedation and anesthesia of ornamental finfish</td>
</tr>
</tbody>
</table>
Extralabel Use

- 21 CFR 530.3 Definitions.

  (a) *Extralabel use* means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.
Legal Extra-label Drug Use (ELDU)

- Veterinarians can authorize use of approved human and animal drugs in food-producing animals for uses not on the label if -
  - No approved product is available for the use
  - A valid Veterinary Client Patient Relationship exists
  - The use is therapeutic (not production)
  - The vet assigns a withdrawal time
  - The vet keeps appropriate records
Limitations of Legal ELDU

- Some drugs are prohibited from extralabel use in food-producing animals - E.g., clenbuterol, chloramphenicol, fluoroquinolones...
- Extralabel use of conditionally approved and indexed products is not permitted.
- Extralabel use of medicated feed is not permitted.

Refer to 21 CFR 530, the regulations for extralabel drug use, for complete information
• Extra-label use of medicated feed is not legal.

• FDA recognized that there are only a few approvals of medicated feeds for minor species and for some species or instances medicated feed is the only practical method to administer treatment.

• In order to have therapeutic options available for treatment of minor species, and to help ensure animal safety and human food safety, FDA intends to exercise enforcement discretion as described in CPG 615.115
CPG 615.115

- CPG = Compliance Policy Guide
- A CPG gives directions to the enforcement part of FDA (inspectors in the field).
- It is a way to allow use under certain specific conditions.
- In short, if you follow this CPG, FDA is unlikely to take enforcement action.
CPG 615.115

• *Just for minor species* (not horses, cattle, pigs, chickens, turkeys, dogs, or cats)

• First published in April 2001
  – Did *not* include VFDs

• Revised CPG published December 2016
  – Includes VFDs
CPG 615.115

• Requires a valid Veterinary Client Patient Relationship

• Extra-label use of medicated feed may be considered for treatment of minor species if:
  – There are no approved treatment options available,
  – The health of animals is threatened, and
  – Suffering or death would result from failure to treat the affected animals
CPG 615.115: General Considerations

- Prior written recommendation with VCPR described in 21 CFR 530
- For minor species & indications not on labeling
- For fish, limited to medicated feeds approved for aquatic species
  - Drugs approved in other dosage forms (e.g. injectable) cannot be added to feed
  - Cannot use drugs approved only for cattle, etc., the drug needs to be approved for an aquatic species
- You cannot change the concentration of the drug in the feed from the approved level
- Only for farmed or confined species (not wildlife)
- Not for production purposes (only when animal health is threatened)
- No promotion or advertising of the ELDU
- Certain drugs specifically prohibited from ELDU (21 CFR 530.41)
CPG 615.115

- CPG includes additional considerations for veterinarian, producer (client), feed mill/distributor, regarding, for example:
  - Withdrawal periods
  - Animal identification
  - Document retention
  - NPDES requirements
January 1, 2017, antimicrobials of medical importance in human medicine and administered in medicated feed or drinking water to food-producing animals transitioned to Veterinary Feed Directive (VFD) or prescription (Rx) status
FDA/CVM Efforts to Address Antimicrobial Resistance

- Microbial food safety assessment is part of approval process for antimicrobials intended for food animals
- National Antimicrobial Resistance Monitoring System
- Collection and reporting of information on antimicrobial sales and distribution
- Education and outreach
- Collaboration with international partners
- Research
- CVM has limited the use of certain cephalosporins and withdrew the approval of fluoroquinolones for use in poultry.
Guidance for Industry #209

The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

• FDA’s overall policy published in 2012
• Limit use of medically-important antimicrobial drugs in food-producing animal to uses that
  – Are considered necessary for animal health (phase out weight gain and feed efficiency uses)
  – Include veterinary oversight/consultation
What Happened Next

• In 2013, FDA published additional guidance (#213) describing how drug companies could align their products with these principles

• Drug companies voluntarily agreed to make changes to their products over a three year time period (by December 2016)

• In 2015, after several opportunities for public comment, FDA revised the Veterinary Feed Directive Regulations
1 January 2017:
Medically important antimicrobials administered in or on medicated feed or in water that were labeled over-the-counter now require an authorization from a licensed veterinarian for use (i.e. are now VFD or Rx).
How Does This Affect You?

- What drugs are included?
- What does a VFD involve?
Scope of the Changes

• Only affects antibiotics that are (meets both conditions):
  – “Medically-Important” – meaning important in human medicine
    • These drugs are listed in Appendix A of GFI #152 – does not include disinfectant type drugs
  – Administered to food producing animals in feed or drinking water
    • Oxytetracycline HCl products approved for fish indication are also approved for drinking water uses for terrestrial animals
    • Other dosage forms (e.g. injectable) are not affected in this transition
<table>
<thead>
<tr>
<th>Rx Drugs</th>
<th>(not all on list may be currently marketed)</th>
</tr>
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<tbody>
<tr>
<td>Federal law restricts this drug to use by or on the order of a licensed veterinarian.</td>
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<tr>
<th>Immersion</th>
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<tr>
<td>OXYmarine™</td>
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<tr>
<td>Pennox 343®</td>
</tr>
<tr>
<td>Terramycin 343® Soluble Powder</td>
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<tr>
<td>Tetroxy® 343</td>
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<tr>
<td>Tetroxy® Aquatic</td>
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<tr>
<th>Injectable</th>
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<tr>
<td>Chorulon®</td>
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</table>
Newly Rx drugs

• These drugs are regulated the same way as other RX veterinary drug dosage form drugs
  – Dispensed the same way as other veterinary RX drugs (such as injectable RX drugs)
    • The prescription can be filled by your vet or by a pharmacist at a distributor.
  – Same types of recordkeeping
  – Same timeline as drugs transitioning to VFD
  – Same enforcement as other RX veterinary dosage form drugs
VFD Drugs
(not all on list may be currently marketed)

“Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian.”

Aquafolor®
Terramycin® 200 for Fish
Romet®-30, Romet®-TC
Sulfamerazine Fish Grade
What is a VFD?
What is a Veterinary Feed Directive?

• It is a *Marketing status* – animal drugs are approved as:
  – Over-the-counter (OTC)
  – Prescription (Rx) (injections, water medications, tablets, etc.), or
  – Veterinary Feed Directive (VFD) (medicated feed)

• This is based on the directions for use and whether (Rx, VFD) or not (OTC) a veterinarian’s knowledge is needed to use the product safely/effectively.
The VFD Order

• A written statement prepared by a veterinarian authorizing distribution of medicated feed.

• Prepared by the veterinarian and given to the client for presentation to the feed mill, or it can go there electronically.

• Vet makes the diagnosis, chooses the medication, determines the dose and duration, notes the withdrawal period, etc. as labeled.

• It must be issued within a valid veterinarian-client-patient relationship (VCPR).
What does a VFD involve?
Requires a Valid Veterinary Client Patient Relationship (VCPR)

• VCPR exists when:
  – A licensed vet has assumed responsibility for making medical judgements for the animal(s)
  – The client has agreed to follow the vet’s instructions
  – The vet knows the animal(s) well enough to make at least a preliminary diagnosis
  – The vet is available for follow up in case of adverse reactions or failure of treatment
What’s a valid VCPR? (continued)

• Veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animals are kept.

• State or Federal definition - See: [http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm460406.htm](http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm460406.htm)
Information the VFD Order must include:

- Vet’s name, address, phone
- Client’s name, address, phone
- Premises animals are located at
- Date issued, date of expiration
- Name of the drug
- Species & production class & approximate number of animals to be treated
- Indication (disease or condition)
And...

- Level of drug in the feed and duration of use
- Withdrawal time, special instructions, cautions
- Number of refills authorized (if permitted by approval)
- An affirmation of intent for combination drugs (no combinations approved at this point for fish)
- Statement: “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.”
- Vet’s signature (electronic or written)
VFD Expiration Date

– Specifies the period of time for which the VFD authorization is valid.
– It is the last day the VFD feed can be fed.
– A VFD feed cannot be fed after the expiration date (i.e., after VFD authorization expires).
– May be specified on the product label; if not – it cannot exceed 6 months after the date of issuance.
– The veterinarian can assign a shorter expiration date.
– Not to be confused with the duration of use (length of time medicated feed should be administered as per the approved label instructions)
Refills?

• Currently, there are no approved VFD drugs that allow refills.

• Means that the vet cannot write on the VFD that you can refill it.

• If you have another outbreak, the vet needs to decide whether or not a new VFD is appropriate.
VFD feed: Producer’s Role

- Establish/maintain a VCPR
- Obtain a VFD order from the veterinarian
- Provide a copy of the VFD order to the feed manufacturer or supplier (unless done by vet)
- Producers who manufacture their own feed must have a VFD before feeding VFD medicated feed and follow manufacturing and record keeping requirements
- Follow the stipulations of the VFD order; otherwise the VFD is not valid and drug use in violation of the law
- Maintain copy of the VFD for 2 years and provide VFD order to FDA upon inspection or request
What do producers need to do?

• Don’t panic, but prepare:
• Establish a Veterinarian-Client-Patient Relationship (VCPR).
• Be sure that the vet understands their needs.
• Determine where they will get the drug from (e.g. feed mill, distributor, etc.)
• Check how to get prescriptions or VFDs to the distributor or feed mill.
What about the feed mills?

• The regulations refer to a “distributor”
  There are two kinds of distributors:
  1. Only distributes VFD feed
  2. Manufactures and distributes VFD Feed

• Distributors must notify FDA:
  – Prior to the first time they distribute animal feed containing a VFD drug
  – Within 30 days of any change of ownership, business name, or business address
For More Information

Visit the CVM website!

- **Aquaculture pages and articles**
- **Animal Drugs@FDA** (approved applications)
- **VFD page**
  - VFD brochures and videos
  - Guidance #120
  - List of VFD distributors & licensed feed mills
- **CPG 615.115**

Send questions to askCVM@fds.hhs.gov
Questions?