My 45-Year Passion for Aquaculture Drug Approvals*

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What I Have Learned... Individuals Needed with a Vision to Initiate, & Facilities to Sustain, the Approval Process
Research Directors with a Vision for Gaining Approvals

Dr. Robert E. Lennon (1959-1972) at Fish Control Laboratory=FCL

Dr. Fred P. Meyer (1973-1990) at FCL, now Upper Midwest Environmental Sciences Center=UMESC
An Initial & Subsequent Research Facility that Could Do the Work

Initially called the Fish Control Laboratory (=FCL, 1959-1978)

Now called the Upper Midwest Environmental Sciences Center (=UMESC, 1978-present)
Researchers & Facilities to
Accomplish the Approval Research

UMESC Researchers & Facilities
What I Have Learned...
You Need a Crisis for People
to be Motivated to Change &
Act
Initial Crisis That Led to first US Aquaculture Drug Approvals (1 of 2)

- 1964—Initial impetus for public funding
  - US Food & Drug Administration (FDA) Center for Veterinary Medicine (CVM) to FWS: “Gain approvals or else!!”

- 1966—FWS survey of public aquaculture

- 1972—FWS’s Fish Control Laboratory (=FCL) designated as lead FWS chemical registration facility with no additional funds or personnel
Initial Crisis That Led to first US Aquaculture Drug Approvals (2 of 2)

- 1974—CVM to FCL (later UMESC): “Go away, we do not know what to do with you” but we did not
- Initial crisis led to 6 *new drugs being approved (1964-1994)—Drug (#label claims)
  - *Formalin (4)
  - *Furanace Capsules®=nifurprynol (1; terminated)
  - *Romet® 30=sulfadimethoxine & ormetoprim (2)
  - *Sulfamerazine in Fish Grade®=sulfamerazine (1; no longer commercially available)
  - *Terramycin® for Fish=oxytetracycline mono-alkyl trimethyl ammonium (8)
  - *Tricaine methanesulfonate (1)
Crisis in 1990 That Led to Accelerated Approvals in USA (1 of 2)

- 1990—CRISIS HAPPENS!!
  - CVM announces results of hatchery survey for chemicals & drugs & indicates need for additional approvals & clarification of usage
  - Joint Subcommittee on Aquaculture establishes working group to deal with crisis & establish chemical categories & priorities
  - CVM provides new leadership toward resolving aquaculture drug approval issues
  - Aquaculture groups were incentivized to support approvals—led to Federal-State Aquaculture Drug Approval Partnership Project, a $30+ million project for 8 drugs
Crisis in 1990 That Led to Accelerated Approvals in USA (2 of 2)

- 1990 crisis led to 4 *new drug & additional label claim approvals (1995-2012)—Drug (#label claims)
  - *Aquaflor®=florfenicol (4)
  - *Chorulon®=human chorionic gonadotropin (1)
  - Formalin (3; additional sponsors)
  - *35% PEROX-AID®=hydrogen peroxide (3)
  - *Oxytetracycline hydrochloride (1; additional sponsors)
  - Terramycin® 200 for Fish=oxytetracycline dihydrate (2) & new formulation
  - Tricaine methanesulfonate (additional sponsor)
What I have Learned...
Factors Essential to Achieve Drug Approvals
Identify Safe & Effective Drugs

- Survey aquaculture industries for needs for health promotion & efficient production

- Identify potential drugs to meet those needs

- Request clarification from regulatory agencies of compound status (i.e., whether the use is a drug, pesticide, or other application)

- Evaluate, prioritize & select compounds identified as drugs for feasibility & immediate possibility for drug approvals
Identify Adequate Resources to Gain Drug Approvals

- Identify & retain committed company sponsors early in the process

- Leverage private sponsor investment with adequate, outside funds to meet the data generating needs

- Identify knowledgeable research researchers & adequate facilities to meet the needs of safety, etc.

- Establish major partnerships

- Identify oversight & coordination entities
Implement the Approval Process

- Develop product development plans
- Consult with regulatory agency on the plans
- Initiate drug approval efforts on selected, prioritized drugs
- Be persistent & engage the regulatory agency
- Do not give up even if it seems hopeless
What I have Learned...
Regulatory Agency Needs to be Engaged & Supportive
Major Factor in US Approval Successes—CVM Leadership (1 of 2)

- Identified compounds that were classified as drugs

- Created Low Regulatory Priority List of 18 Unapproved Drugs

- Created “Compassionate” investigational permits

- Supported creation & funding of National Aquaculture NADA Coordinator

- Developed regulations & policies—clarified approval path

- Committed funds for research

- Developed Aquaculture Drugs Team
Major Factor in US Approval Successes—CVM Leadership (2 of 2)

- Supported Minor Use & Minor Species Animal Health Act of 2004 (MUMS)—benefited aquaculture drug sponsors greatly
  - 79 of 102 designations=aquaculture drugs which allows for 7 years of marketing exclusivity
  - Indexing to cover non-food fish species=2 Indexed
  - Conditional approvals=1 Conditional approval
  - Grants (started summer 2009)

- Animal Drug User Fee Act (ADUFA)—exempted sponsors of drugs for minor species from all fees (while benefiting from the fees)
What I have Learned...
There Will be Obstacles to Drug Approvals
**26 Drugs Dropped >1995**

- Amoxicillin
- Benzocaine
- Bronopol (Pyceze®)
- Calcein
- Crude carp pituitary
- Cutrine-Plus®
- Diquat dibromide
- Earth-Tec®
- Enrofloxacin
- 17 β-estradiol
- Fumagillin
- MelaFix®
- Metomidate
- MS-222
- Neomycin sulfate
- Ovaprim®
- Potassium permanganate
- Praziquantel
- Quinine
- ReproBoost®
- Sarafloxacin
- Sea lice control (4)
- Trichlorfon
Major Factors that Hinder US Drug Approval Process (1 of 3)

- LACK OF FUNDING/COMMITTED SPONSORS TO MEET ALL DATA REQUIREMENTS FOR APPROVAL
Major Factors that Hinder US Drug Approval Process (2 of 3)

- Regulatory changes
  - Antimicrobial resistance issues
- Effluent issues
  - Establishment of national & international guidelines delayed approvals until 2004
- Additional studies required & not anticipated
- Changes in personnel=new regulations & requirements
Major Factors that Hinder US Drug Approval Process (3 of 3)

- Study issues
  - Negative results in toxicology studies
  - Studies take longer than anticipated
  - Costs increase dramatically

- Changes in study personnel & laboratory requirements necessitating facility renovation

- Predictions on timetables, costs & requirements are never accurate
What I have Learned...
If One Persists, Aquaculture Drug Approvals Will Come
9 Drugs Approved for US Aquaculture

Aquaflo®
- Catfish – enteric septicemia
- FW salmonids – furunculosis, coldwater disease

Chorulon®
- All fish – spawning aid

Formalin (3 sponsors)
- FW fish – protozoans, monogeneans
- FW eggs – saprolegniasis
- Penaeid shrimp – protozoans

Oxytetracycline hydrochloride (5 sponsors)
- Fry and fingerling – marking

35% PEROX-AID®
- FW eggs – saprolegniasis
- FW salmonids – bacterial gill disease
- Coolwater fish & CCF – columnaris disease

Romet® 30 and TC
- Catfish – enteric septicemia
- Salmonids – furunculosis

Sulfamerazine in Fish Grade®
- Trouts - furunculosis

Terramycin® 200 for Fish
- Catfish – hemorrhagic septicemia, pseudomonas disease
- Salmonids – furunculosis, coldwater disease, hemorrhagic septicemia, pseudomonas disease
- Oncorhynchus mykiss – columnaris disease
- Lobster - Gaffkemia
- Pacific salmon--marking

Tricaine methanesulfonate (2 sponsors)
- 4 fish families – sedative
2 Indexed Drugs for US Aquaculture

- **Ovaprim®** (salmon gonadotropin releasing hormone analog)
  - Ornamental fish – spawning aid
- **Aquacalm®** (metomidate)
  - Ornamental fish – sedative & anesthetic
# 48-Year History of US Aquaculture Approvals & Beyond

<table>
<thead>
<tr>
<th>Dates</th>
<th>NADAs</th>
<th>New Drugs</th>
<th>Label Claims</th>
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<tbody>
<tr>
<td>1964-1994 (31 years)</td>
<td>11</td>
<td>6 (1 terminated)</td>
<td>17</td>
</tr>
<tr>
<td>1995-2012 (17 years)</td>
<td>17</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total Approvals</strong></td>
<td><strong>28 NADAs Approved</strong></td>
<td><strong>10 New Drugs Approved</strong></td>
<td><strong>31 Label Claims Approved</strong></td>
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<td><strong>(48 years—1964-2012)</strong></td>
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<tr>
<td>Near Future (1-2 years)</td>
<td>5+</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Under Development</td>
<td>4+</td>
<td>5</td>
<td>10+</td>
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<tr>
<td><strong>Grand Totals Anticipated</strong></td>
<td><strong>37+ NADAs Anticipated</strong></td>
<td><strong>20 New Drugs Anticipated</strong></td>
<td><strong>58+ Label claims Anticipated</strong></td>
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Finally, After 48 Years, US Aquaculture has:

(1 of 2)

- An adequate medicine chest that is still expanding
- New laws, regulations, & guidelines in place that help the data generating partners & prospective sponsors to proceed toward aquaculture drug approvals
- Numerous CVM functions, positions, & processes that help/helped approval processes
Finally, After 48 Years, US Aquaculture has:

(2 of 2)

- Maturation of the data-generating partners relative to interaction with sponsors & CVM & understanding of data requirements & studies

- Knowledgeable & engaged pharmaceutical & chemical sponsors

- Active & supportive aquaculture associations & companies

- Identification of additional sources of funding
  - Recently, MUMS Grants
The Future for Aquaculture Drug Approvals

- There will be
  - Additional approvals
    - New innovative compounds; e.g., essential oils
    - Only demonstrated safe drugs will move forward
  - Innovative delivery methods to reduce exposure to non-target organisms, e.g., encapsulation or matrices for delivery systems
  - Integrated disease management technologies
  - Continued challenges to use of drugs & chemicals in aquaculture
Questions?