Data to Support FDA approval of: AQUI-S®20E and BENZOAK®

Potential Immediate-Release Sedatives

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What is an Ideal Sedative?

- Induction time of <15 min (preferably <3 min)
- Short recovery time (< 5 min)
- Nontoxic to fish, large safety factor
- Inexpensive
- Easy to use
- Safe to humans during normal use
- **No withdrawal time**
  - Immediate release
Immediate Release Sedatives?

• **AQUI-S®20E**
  - AQUI-S New Zealand, Ltd.
  - 10% eugenol
  - 3 d withdrawal period
  - Only available under INAD 11-741
  - $299 for 1 L (approximation)

• **BENZOAK®**
  - Frontier Scientific, Inc.
  - 20% benzocaine
  - 3 d withdrawal period
  - Only available under INAD 11-740
  - $385 for 1 L (approximation)

$450 for 1 kg of Finquel and $350 for 1 kg of Tricaine-S
Easy to Use?

- Yes!
- Both can be pipetted directly into a tub of water
  - Then stir to mix
Efficacy Studies

- Small mountain of data required
  - To demonstrate efficacy
  - To support FDA approval
- AADAP and partners have completed
  - 20 pivotal studies
  - 14 high quality supportive studies
- All pivotal studies
  - Conducted to under FDA/CVM approved research study protocols
Experimental Design - Pivotal Studies

- Masking
- Positive control
  - MS-222
- Dose-verification of exposure solutions
  - ±20% of target dose
- For each species of fish:
  - 30 individual fish tested
- Data collected:
  - Time to handleable
  - Time to recover from the handleable stage
  - Behavior during and after sedation
  - Temperature, dissolved oxygen, and pH
High Quality Supportive Studies

• Approved protocol used as a guideline
  – However, one or more of the criteria in the study protocol are not followed:
    • Fewer fish used
    • No dose-verification
    • No positive control
    • No masking
Experimental Design - Pivotal Studies

- CVM wants efficacy of a product to be evaluated at the low end of the use range
  - Only one concentration tested for each of the temperature groups of fish
    - Selected a concentration that would sedate fish to handleable in <3 min
What is Handleable?

- Similar to Stages 3 – 4 as described by Summerfelt and Smith (1990)
- Specifically:
  - Lose of equilibrium
  - Fish can be easily
    - Caught by hand,
    - Placed on a measuring board
    - Measured for length
    - Little to no movement
What is Recovered?

- Fish regains normal equilibrium in the water column
- Fish resumes normal swimming behavior
- Fish can avoid obstacles placed in path

*Note: This is a very conservative measurement of time to recover*
Fish Species

- **Salmonids:**
  - Rainbow trout, cutthroat trout, brown trout, lake trout, and Arctic char
- **Coolwater:**
  - Yellow perch, walleye, common carp, and fathead minnows
- **Warmwater:**
  - Blue catfish, hybrid striped bass, and channel catfish
## Data Summary

<table>
<thead>
<tr>
<th>Species</th>
<th>Product</th>
<th>Sedative Concentration</th>
<th>Water Temperature</th>
<th>Mean Handleable</th>
<th>Mean Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmonids</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>AQUI-S®20E</td>
<td>250 ppm</td>
<td>13.2°C</td>
<td>1.8 min (1.3 – 2.5)</td>
<td>5.5 min (2.6 – 11.1)</td>
</tr>
<tr>
<td></td>
<td>BENZOAK®</td>
<td>200 ppm</td>
<td>13.9°C</td>
<td>1.8 min (1.0 – 2.9)</td>
<td>3.8 min (0.9 – 9.2)</td>
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<tr>
<td><strong>Coolwater</strong></td>
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</tr>
<tr>
<td></td>
<td>AQUI-S®20E</td>
<td>400 ppm</td>
<td>18.2°C</td>
<td>2.5 min (1.5 – 5.0)</td>
<td>9.9 min (4.4 – 16.8)</td>
</tr>
<tr>
<td></td>
<td>BENZOAK®</td>
<td>400 ppm</td>
<td>18.0°C</td>
<td>2.1 min (1.1 – 3.3)</td>
<td>9.0 min (4.8 – 18.3)</td>
</tr>
<tr>
<td><strong>Warmwater</strong></td>
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<tr>
<td></td>
<td>AQUI-S®20E</td>
<td>600 ppm</td>
<td>24.3°C</td>
<td>1.3 min (0.6 – 2.4)</td>
<td>7.6 min (5.1 – 10.8)</td>
</tr>
<tr>
<td></td>
<td>BENZOAK®</td>
<td>750 ppm</td>
<td>24.7°C</td>
<td>1.3 min (0.7 – 2.5)</td>
<td>6.2 min (3.7 – 9.6)</td>
</tr>
</tbody>
</table>

*Note: Only data from pivotal studies are shown*
Effect of Size and Temperature

- High Quality Supportive Study
  - Rainbow trout
  - One sedative and concentration
    - 250 ppm AQUI-S®20E (25 ppm eugenol)
  - Two life-stages
    - Adult, 40 cm and 0.9 kg
    - Juvenile, 17 cm and 55 g
  - Two water temperatures
    - 10 or 16°C
Overview of Data

- **Adult_cold**: 1.7 min, 6.4 min
- **Juvenile_cold**: 1.8 min, 4.7 min
- **Adult_warm**: 1.3 min, 4.8 min
- **Juvenile_warm**: 1.3 min, 3.6 min

Graph showing times for different categories in minutes.
Summary

• Fish become handleable in an ‘ideal’ period of time
  – Less than 3 min

• Fish recover faster after exposure to BENZOAK® than AQUI-S®20E
  – Recovery times ‘less-than-ideal’,
  – However, a conservative measure of recovery was used

• Both products are easy to use and work well
  – Add products directly to tub of water and stir
  – Sedated a variety of species, life-stages and water temperatures

• No fish died during or after any studies
  – Normal behavior
    • Some piping
    • Some head shaking
A Big Thanks To.....

- Fort Richardson State Fish Hatchery
  - Alaska Department of Fish & Game
- Dr. Jesse Trusenski and students
  - Southern Illinois University – Carbondale
- Alan Johnson
  - Iowa DNR Rathbun Fish Culture Research Facility
- Jeff Meinertez and staff
  - USGS Upper Midwest Environmental Sciences Center
- Hatchery staff
  - USFWS Bozeman Fish Technology Center
Status

• Results from 7 studies
  – Submitted to CVM for review

• Results from the rest of the studies
  – Will be submitted this winter

• Request that the effectiveness technical section be considered complete
  – No more data necessary to demonstrate effectiveness

• Conduct studies to demonstrate that the effective doses are safe
  – Three studies required
Questions??